alone could elicit a conditioned hyperthermia from the rat. An effect which may be relevant to the finding of this experiment is that drug-induced changes in body temperature (hyperthermia or hypothermia) in animals can also be classically conditioned [Cunningham et al., 1984].

We have conducted experiments to investigate whether the effects of low-level RFR on psychoactive drug actions and central cholinergic activity can be classically conditioned to cues in the exposure environment. Classical conditioning of drug effects with environmental cues as the conditioned stimulus have been reported and such conditioned responses have been suggested to play a role in drug response, abuse, tolerance, and withdrawal [Le et al., 1979; Siegel, 1977, Siegel et al., 1982, Wikler, 1973a; Woods et al., 1969]. We found that the effects of RFR on amphetamine-induced hyperthermia and cholinergic activity in the brain can be classically conditioned to environmental cues [Lai et al., 1986b, 1987c].

In earlier experiments, we reported that acute (45 min) exposure to 2450-MHz RFR at average whole body SAR of 0.6 W/kg attenuated amphetamine-induced hyperthermia [Lai et al., 1983] and decreased HACU in the frontal cortex and hippocampus [Lai et al., 1987b] in the rat. In the conditioning experiments, rats were exposed to 2450-MHz pulsed RFR (2 μs pulses, 500 pps, 1.0 mW/cm^2, SAR 0.6 W/kg) in ten daily 45-min sessions. On day 11, animals were sham-exposed for 45 min and either amphetamine-induced hyperthermia or high-affinity choline uptake (HACU) in the frontal cortex and hippocampus was studied immediately after exposure. In this paradigm the RFR was the unconditioned stimulus and cues in the exposure environment were the neutral stimuli, which after repeated pairing with the unconditioned stimulus became the conditioned stimulus. Thus on the 11th day when the animals were sham-exposed, the conditioned stimulus (cues in the environment) alone would elicit a conditioned response in the animals. In the case of amphetamine-induced hyperthermia [Lai et al., 1986b], we observed a potentiation of the hyperthermia in the rats after the sham exposure. Thus, the conditioned response (potentiation) was opposite to the unconditioned response (attenuation) to RFR. This is known as 'paradoxical conditioning' and is seen in many instances of classical conditioning [cf. Mackintosh, 1974]. In addition, we found in the same experiment that, similar to the unconditioned response, the conditioned response could be blocked by the drug naloxone, implying the involvement of endogenous opioids. In the case of RFR-induced changes in cholinergic activity in the brain, we [Lai et al., 1987c] found that conditioned effects also occurred in the brain of the rat after the session of sham exposure on day 11. An increase in HACU in the hippocampus (paradoxical conditioning) and a decrease in the frontal cortex were observed. In addition, we found that the effect of RFR on hippocampal HACU habituated after 10 sessions of exposure, i.e., no significant change in HACU in the hippocampus was observed in animals exposed to the RFR on day 11. On the other hand, the effect of RFR on frontal cortical HACU did not habituate after the repeated exposure.

An explanation for the paradoxical conditioning phenomenon was given by Wikler [1973b] and Eikelboom and Stewart [1982]. The direction of the conditioned response (same as or opposite to the unconditioned response) depends on the site of action of the unconditioned stimulus, whether it is on the afferent or efferent side of the affected neural feedback system. Thus, in order to further understand the neural mechanisms of the conditioned effects, the site of action of RFR on the central nervous system has to be identified.

Little work has been done to investigate the effects of RFR on memory functions. We [Lai et al., 1989b] studied the effect of acute (20 or 45 min) RFR exposure (2450-MHz, 1 mW/cm^2, SAR 0.6W/kg) on the rats' performance in a radial-arm maze, which measures spatial learning and memory functions. The maze consists of a central circular hub with arms radiating out like

the spokes of a wheel. In this task, food-deprived animals are trained to explore the arms of the maze to obtain food reinforcement at the end of each arm. In each session they have to enter each arm once and a reentry is considered as an error. This task requires the so called 'working memory', i.e., the rat has to remember the arms it has already entered during the course of a session. Working memory requires the functions of the cholinergic innervations in the frontal cortex and hippocampus [Dekker et al., 1991; Levin, 1988]. Both have been shown to be affected by acute RFR exposure [Lai et al., 1987b]. We [Lai et al., 1989b] found that acute (45 min) exposure to RFR before each session of maze running significantly retarded the rats' abilities to perform in the maze. They made significantly more errors than the sham-exposed rats. This result agrees with the neurochemical finding that 45 min of RFR exposure decreased the activity of the cholinergic systems in the frontal cortex and hippocampus of the rats [Lai et al., 1987b]. However, 20 min of RFR exposure, which increased cholinergic activity in the brain, did not significantly affect maze performance. Apparently, increase in cholinergic activity cannot further improve the performance, since the neural systems involved in the memory function may be working at optimal levels under normal conditions. In a recent experiment [Lai et al., 1993], we have shown that the microwave-induced working memory deficit in the radial-arm maze was reversed by pretreating the rats before exposure with the cholinergic agonist physostigmine or the opiate antagonist naltrexone, whereas pretreatment with the peripheral opiate antagonist naloxone methiodide showed no reversal of effect. These data indicate that both cholinergic and endogenous opioid neurotransmitter sysatems inside the central nervous system are involved in the microwave-induced spatial memory deficit.

Several studies have investigated the effect of RFR on discrimination learning and responding. Hunt et al. [1975] trained rats to bar press for saccharin water rewards in the presence (5 sec duration) of a flashing light and not to respond in the presence of a tone (unrewarded). After 30 min of exposure to 2450-MHz RFR, modulated at 20 Hz and at SAR of 6.5 or 11.0 W/kg, rats made more misses at the presence of the light, but there were no significant changes in the incidences of bar-pressing errors when the tone was on. The effect was more prominent at the higher dose rate. Galloway [1975] trained rhesus monkeys on two behavioral tasks to obtain food reward. One was a discrimination task in which the monkey had to respond appropriately depending on which of the two stimuli was presented. The other task was a repeated acquisition task in which a new sequence of responses had to be learned everyday. After training, the animals were irradiated with continuous-wave 2450-MHz RFR applied to the head prior to each subsequent behavioral session. The integral dose rates varied from 5-25 W. Some of these dose rates caused convulsions in the monkeys. The radiation was shown to exert no significant effect on the discrimination task, whereas a dose-dependent deficit in performance was observed in the repeated acquisition task. Cunitz et al., [1979] trained two rhesus monkeys to move a lever in different directions depending on the lighting conditions in the exposure cage in order to obtain food reinforcement on a fixed ratio schedule. After the animals' performance had reached a steady and consistent level, they were irradiated at the head with continuous-wave 383-MHz RFR at different intensities in subsequent sessions. Radiation started 60 min before and during a session of responding. The authors reported a decrease in the rate of correct responding when the SAR at the head reached 22-23 W/kg. In another study, Scholl and Allen [1979] exposed rhesus monkeys to continuous-wave 1200-MHz RFR at SARs of 0.8-1.6 W/kg and observed no significant effect of the radiation on a visual tracking task.

de Lorge [1976] trained rhesus moneys on an auditory vigilance (observing-response) task. The task required continuous sensory-motor activities in which the monkeys had to coordinate

their motor responses according to the stimulus cues presented. In the task the monkeys had to press the right lever that produced either a 1070-Hz tone for 0.5 sec or a 2740-Hz tone. The 1070-Hz tone signalled an unrewarded situation. Pressing a left lever when the 2740-Hz tone was on would produce a food reward. Presentation of the higher frequency tone was on a variable interval schedule. After the monkeys had learned to perform the task at a steady level, they were irradiated with 2450-MHz RFR of different intensities. Decreased performance and increased latency time in pressing the left lever were observed when the power density at the head was at 72 mW/cm^2. The deficits could be due to an increase in colonic temperature after exposure to the high intensity RFR.

de Lorge [1979] trained squirrel monkeys to respond to another observing-response task using visual cues. After learning the task, the animals were exposed to 2450-MHz RFR (sinusoidally modulated at 120 Hz) for 30 or 60 min at different power densities (10-75 mW/cm^2) in subsequent sessions. Their performances were disrupted at power densities >50 mW/cm^2. The disruption was power density-dependent and occurred when the rectal temperatures increased more than 1 ^oC. In a more recent experiment, de Lorge [1984] studied rhesus monkeys trained on the auditory vigilance task and the effects of exposure to RFRs of different frequencies (225, 1300, and 5800 MHz). Reduction in performance was observed at different power density thresholds for the frequencies studied: 8.1 mW/cm^2 (SAR 3.2 W/kg) for 225 MHz, 57 mW/cm^2 (SAR 7.4 W/kg) for 1300 MHz, and 140 mW/cm^2 (SAR 4.3 W/kg) for 5800 MHz. de Lorge concluded that the behavioral disruption under different frequencies of exposure was more correlated with change in body temperature. Disruption occurred when the colonic temperature of the animal had increased by 1 ^oC.

Many studies have investigated the effects of RFR on reinforcement schedule-controlled behavior. Sanza and de Lorge [1977] trained rats on a fixed interval schedule for food pellets. After 60 min of exposure to 2450-MHz RFR (modulated at 120 Hz) at 37.5 mW/cm^2, a decrease in response with an abrupt onset was observed. This effect was more pronounced in rats with a high base line of response rate on the fixed interval schedule. No significant effect on response was observed at power densities of 8.8 and 18.4 mW/cm^2.

D'Andrea et al. [1976] trained rats to bar-press for food at a variable interval schedule. After a constant responding rate was attained, the animals were irradiated with continuous- wave RFRs of 360, 480, or 500 MHz. Bar-press rates were decreased only when the rats were exposed to the 500-MHz radiation at a SAR of approximately 10 W/kg. The animals also showed significant signs of heat stress. In a subsequent study [D'Andrea et al., 1977] RFRs of different frequencies and intensities were studied on their effect on bar-pressing rate on a variable interval schedule. It was found that the latency time of stoppage to respond after the radiation was turned on correlated with the rate of rise in body temperature of the animal. These experiments definitely demonstrated the thermal effect of RFR on operant behavior.

Gage [1979a] trained rats on a variable interval schedule for food reinforcement. Different groups of rats were exposed overnight (15 h) to continuous-wave 2450-MHz RFR at either 5, 10, or 15 mW/cm^2. Responses were tested immediately after exposure. No significant difference in performance was found between the RFR- and sham-exposed rats when exposure was done at an ambient temperature of 22 ^oC. However, a power density- dependent reduction in response rate and increase in response duration was found in the RFR-exposed rats when the irradiation was carried out at 28 ^oC. At the higher ambient temperature, heat dissipation from the body was less efficient and the exposed rats had higher body temperatures postexposure.

Lebovitz [1980] also studied the effects of pulsed 1300-MHz (1 μs pulses, 600 pps) RFR on rats bar-pressing on a fixed interval schedule for food reinforcement. Both food reinforced bar presses and unrewarded bar presses during the intervals were studied. No significant effect was detected in both types of response at SAR of 1.5 W/kg. However, at 6 W/kg, there was a slight reduction in rewarded bar presses and a large reduction in unrewarded bar presses. The authors concluded that the unrewarded behavior was more susceptible to the effect of RFR than the rewarded behavior. Another related experiment was reported by Sagan and Medici [1979] in which water-deprived chicks were given access to water on fixed intervals irrespective of their responses. During the time between water presentations the chicks showed an increase in motor activity known as 'interim behavior'. Exposure to 450-MHz RFR amplitude-modulated at 3 and 16 Hz at power densities of either 1 or 5 mW/cm^2 during session had no significant effect on the 'interim behavior'.

Effects of RFR on complex operant response sequence and reinforcement schedules were studied in various experiments. de Lorge and Ezell [1980] tested rats on a vigilance behavioral task during exposure to pulsed 5620-MHz RFR and then to pulsed 1280-MHz RFR. In this task, rats had to discriminate two tones in order to press one of two bars appropriately for food reinforcement. Behavioral decrement was observed at an SAR of 2.5 W/kg with the 1280-MHz radiation, but at 4.9 W/kg with the 5620-MHz radiation. Gage [1979b] trained rats to alternate responses between 2 levers at 11-30 times for a food reinforcement. Decrement in response rates was observed after 15 h of exposure to continuous-wave 2450-MHz RFR at 10, 15, and 20 mW/cm^2 (0.3 W/kg per mW/cm^2).

Thomas et al. [1975] trained rats to bar press on two bars: a fixed ratio of 20 on the right bar (20 bar presses produced a food pellet reward) and differential reinforcement of low rate (DRL) on the left bar (bar presses had to be separated by at least 18 sec and no more than 24 sec to produce a reward). There was a time-out period between schedules, i.e., no reinforcement available for responding. Animals were tested 5-10 min after 30 min of exposure to either continuous-wave 2450-MHz, pulsed 2860-MHz (1 μs pulses, 500 pps) or pulsed 9600-MHz (1 μs pulses, 500 pps) RFR at various power densities. An increase in DRL response rate was observed with 2450-MHz radiation >7.5 mW/cm^2 (SAR 2.0 W/kg), 2860-MHz RFR >10 mW/cm^2 (2.7 W/kg), and 9600-MHz RFR >5 mW/cm^2 (SAR 1.5 W/kg). A decrease in the rate of response at the fixed ratio schedule was seen in all three frequencies when the power density was greater than 5 mW/cm^2. In addition, an increase in response rate was observed during time-out periods under irradiation of the three frequencies of RFR at greater than 5 mW/cm^2.

In another study, Thomas et al. [1976] trained rats to bar press on a tandem schedule using 2 bars. Pressing the right bar for at least 8 times before pressing the left bar would give a food pellet reward. A power density-dependent decrease in the percentage of making 8 or more consecutive responses on the right bar before pressing the left bar was observed in the animals after 30 min of exposure to pulsed 2450-MHz RFR (1 μs pulses, 500 pps) at power densities of 5, 10, and 15 mW/cm^2.

Schrot et al [1980] also trained rats to learn a new daily sequence of pressing of three bars for food reinforcement. An increased number of errors and decreased learning rates were observed in the animals after 30 min of exposure to pulsed 2800-MHz RFR (2 μs pulses, 500 pps) at average power densities of 5 and 10 mW/cm^2 (SARs 0.7 and 1.7 W/kg, respectively). No significant effect on performance was observed at power densities of 0.25, 0.5, and 1 mW/cm^2.

Several studies investigated the effects of chronic RFR exposure on schedule controlled-behavior. Mitchell et al. [1977] trained rats to respond on a mixed schedule of reinforcement

(FR-5 EXT-15 sec), in which 5 responses would give a reward and then a 15 sec lapse time (extinction period) was required before a new response would be rewarded. In addition, the schedule of reinforcement was effective when a lamp was on, while no reinforcement was given when the lamp was off. Rats were then exposed to 2450-MHz RFR (average SAR 2.3 W/kg) for 22 weeks (5 h/day, 5 days/week) and tested at different times during the exposure period. The RFR-exposed rats showed higher responses during the extinction period, indicating poorer discrimination of the response cues. In another also pretrained task, rats had to press a bar to postpone the onset of unsignalled electric foot-shocks (unsignalled avoidance paradigm). No significant difference in performance of this task was observed between the RFR- and sham-exposed animals.

Two series of well-designed experiments were run by D'Andrea et al. [1986a,b] to investigate the effects of chronic RFR exposure on behavior. In one experiment, rats were exposed for 14 weeks (7 h/day, 7 days/week) to continuous-wave 2450-MHz RFR at 2.5 mW/cm^2 (SAR 0.7 W/kg). Decrease in the threshold of electric foot shock detection (i.e., increase in sensitivity) was observed in the irradiated rats during the exposure period. Increased open-field exploratory behavior was observed in the rats at 30 days postexposure. After exposure, the rats were trained to bar press on an interresponse time criterion (IRT). In this schedule, the animals had to respond within 12 to 18 sec after the previous response in order to receive a food reward. Radiofrequency radiation exposed rats emitted more responses during the training period. When the training was completed, the RFR-exposed rats had lower efficiency in bar-pressing to obtain food pellets, i.e., they made more inappropriate responses and received fewer food pellets than the sham-exposed rats during a session. In a signalled two-way active avoidance shuttlebox test, the RFR-exposed rats showed less avoidance response than the sham-exposed rats during training; however, no significant difference in responses in the shuttlebox test was detected at 60 days after exposure between the RFR- and sham-exposed animals. In another series of experiments, rats were exposed to 2450-MHz RFR at 0.5 mW/cm^2 (SAR 0.14 W/kg) for 90 days (7 h/day, 7 days/week). Open-field behavior, shuttlebox performance, and IRT schedule-controlled bar-pressing behavior for food pellets were studied at the end of the exposure period. A small deficit in shuttlebox performance and increased rate of bar-pressing were observed in the RFR exposed rats. Summarizing the data from these two series of experiments [D'Andrea et al., 1986a,b], D'Andrea and his co-workers concluded that the threshold for the behavioral and physiological effects of chronic RFR exposure in the rats studied in their experiments occurred between the power densities of 0.5 mW/cm^2 (SAR 0.14 W/kg) and 2.5 mW/cm^2 (SAR 0.7 W/kg).

D'Andrea et al. [1989] recently studied the behavioral effects of high peak power RFR pulses of 1360-MHz. Rhesus monkeys performing on a complicated reinforcement-schedule involving time-related behavioral tasks (inter-response time, time discrimination, and fixed interval responses) were exposed to high peak power RFR (131.8 W/cm^2 rms, pulse repetition rate 2-32 Hz). No significant disturbance in performance was observed in the monkeys.

Akyel et al. [1991] also studied the effects of exposure to high peak power RFR pulses on behavior. In their experiment, rats pretrained to bar-press for food reinforcement on either fixed ratio, variable interval, or DRL schedule were exposed for 10 min to 1250-MHz pulses. Each pulse (10 μs width) generated a whole body specific absorption of 2.1 J/kg, which corresponds to a whole body average SAR of 0.21 mW/kg. The pulse rate was adjusted to produce different total doses (0.5-14 kJ/kg). Only at the highest dose (14 kJ/kg), stoppage of responding was observed after exposure, when the colonic temperature was increased by ~2.5 ^oC. Responding

resumed when colonic temperature returned to within 1.1 ^{o}C above the preexposure level. When responding resumed, the response rates on the fixed ratio and variable interval schedules were below the preexposure base line level. Responses on the DRL schedule were too variable to allow a conclusion to be drawn. The authors concluded that the effect of the high peak power RFR pulses on schedule-controlled behavior was due to hyperthermia.

Behavior conditioning using different reinforcement schedules generates stable base line responses with reproducible patterns and rates. The behavior can be maintained over a long period of time (hrs) and across different experimental sessions. Thus, schedule-controlled behavior provides a powerful means for the study of RFR-behavior interaction in animals. On the other hand, the behavior involves complex stimulus-response interactions. It is difficult to conclude from the effects of RFR on schedule-controlled behavior the underlying neural mechanisms involved.

In a sense, these studies of RFR are similar to those of psychoactive drugs. A large volume of literature is available on the latter topic. A review of the literature on the effects of psychoactive drugs on schedule-controlled behavior reveals the complexity of the interaction and the limitation in data interpretation. In general, the effects of psychoactive drugs on schedule-controlled behavior is dose-dependent. In many cases, especially in behavior maintained by positive reinforcement, an inverted-U-function has been reported, i.e., the behavior is increased at low doses and decreased at high doses of the drug. In addition, the way that a certain drug affects schedule-controlled behavior depends on three main factors: (a) the base line level and pattern of responding of the animal: a general rule is that drugs tend to decrease the rate when the base line responding rate is high and vice versa. This is known as rate-dependency and is true with psychomotor stimulants, major and minor tranquilizers, sedative-hypnotics, and narcotics; (b) the schedule of reinforcement: in addition to its effect on the base line responding rate, a reinforcement schedule can have other specific effects on responses. For example, amphetamine has different effects on responses maintained on DRL schedule and punishment-suppressed responding schedule, even though both schedules generate a similar low response rate; and (c) the stimulus-control involved in the study: e.g., responses maintained by electric shock are more resistant to drug effects than responses maintained by positive reinforcers. On the other hand, some drugs have differential effects on signalled-avoidance versus continuous avoidance responding.

Thus, to fully understand the effect of RFR, the parameters of the radiation (different dose rates, frequency, duration of exposure, etc.), different reinforcement-schedules, and conditioning procedures have to be carefully studied and considered. However, there is evidence that the above determining factors on schedule-controlled behavior may also hold in the case of RFR. Exposure to RFR caused a decrease in response rate when a variable interval schedule that produces a steady rate of responding was used [D'Andrea et al., 1976; 1977; Gage, 1979a], and an increase in responding when the DRL-schedule of reinforcement was used [Thomas et al., 1975]. This may reflect the rate-dependency effect. On the other hand, stimulus control as a determinant of response outcome was seen in the study of Lebovitz [1980] when unrewarded responses were disrupted more by RFR than rewarded responses, and the study of Hunt et al. [1975] that showed the reverse relationship. In the former experiment a fixed interval schedule was used, whereas in the latter a discrimination paradigm was studied.

Another related point is that most psychoactive drugs affect body temperature. Stimulants cause hyperthermia, barbiturates cause hypothermia, and narcotics have a biphasic effect on body temperature (hyperthermia at low doses and hypothermia at high doses). It is not

uncommon to observe a change of 2-3 ^{o}C within 30 min after a drug is administered. However, in reviewing the literature, there is no general correlation between the effects of the drugs on body temperature and schedule-controlled behavior. Thus, body temperature may not be an important factor in an animal's responding under schedule-controlled behavior, at least in the case of psychoactive drugs. On the contrary, some of the experiments described above strongly suggest the role of hyperthermia on the RFR effect on the behavior. Perhaps, a sudden and large increase in body temperature as in the case of RFR can have a major effect on responding.

Generally speaking, when effects were observed, RFR disrupted operant behavior in animals such as in the cases of discrimination responding [de Lorge and Ezell, 1980; Hunt et al., 1975; Mitchell et al., 1977], learning [Lai, 1989b; Schrot et al., 1980], and avoidance [D'Andrea et al., 1986a,b]. This is especially true when the task involved complex schedules and response sequence. In no case has an improvement in operant behavior been reported after RFR exposure. It is interesting that only disruptions in behavior by RFR exposure are reported. In the studies on EEG, both excitation (desynchronization) and depression (synchronization) have been reported after exposure to RFR [Bawin et al., 1979; Chizhenkova, 1988; Chou et al., 1982b; Dumansky and Shandala, 1976; Goldstein and Sisko, 1974; Dumansky and Shandala, 1976; Takeshima et al., 1979]. Motor activity has also been reported to increase [D'Andrea et al., 1979, 1980; Hunt et al., 1975; Mitchell et al., 1977; Rudnev et al., 1978] and decrease [Johnson et al., 1983; Mitchell et al., 1988; Moe et al., 1976; Rudnev et al., 1978] after RFR exposure. If these measurements can be considered as indications of electrophysiological and behavioral arousal and depression, improvement in operant behavior should occur under certain conditions of RFR exposure. This is especially true with avoidance behavior. Psychomotor stimulants that cause EEG desynchronization and motor activation improve avoidance behavior, whereas tranquilizers that have opposite effects on EEG and motor activity decrease avoidance behavior.

GENERAL DISCUSSION

After reviewing the studies on the effects of RFR on the central nervous system, one obvious question comes to my mind: "What is the mechanism responsible for the effects reported?" In most cases, especially the in vivo studies in which high intensities of irradiation were used resulting in an increase in body temperature, thermal effect is most likely the answer. Even in cases when no significant change in body temperature was detected, thermal effect cannot be excluded. An animal can maintain its body temperature by actively dissipating the heat load from the radiation. Activation of thermoregulatory mechanisms can lead to neuro-chemical, physiological, and behavioral changes. Temperature can be better controlled during in vitro studies. Uneven heating of the sample can still generate temperature gradients, which may affect the normal responses of the specimen studied. However, several points raised by some experiments suggest that the answer is not a simple one. They are: (a) 'Heating controls' do not produce the same effect of RFR [D'Inzeo et al., 1988; Seaman and Wachtel, 1978; Synder, 1971; Johnson and Guy, 1971; Wachtel et al., 1975]; (b) Window effects are reported [Bawin et al., 1975, 1979; Blackman et al., 1979, 1980a,b, 1989; Chang et al., 1982; Dutta et al., 1984, 1989, 1992; Lin-Liu and Adey, 1982; Oscar and Hawkins, 1977; Sheppard et al., 1979]; (c) Modulated or pulsed RFR is more effective in causing an effect or elicits a different effect when compared with continuous-wave radiation of the same frequency [Arber and Lin, 1985; Baranski, 1972; Frey et al., 1973, 1975; Oscar and Hawkins, 1977; Sanders et al., 1983]; (d) Different

frequencies of RFR produce different effects [D'Andrea et al., 1979, 1985; de Lorge and Ezell, 1980; Sanders et al., 1984; Thomas et al., 1975]; and (e) Different exposure orientations or systems of exposure produce different effects at the same average whole body SAR [Lai et al., 1984a, 1988].

I think most of these effects can be explained by the following factors:

1. The physical properties of RFR absorption in the body and the mechanisms by which RFR affects biological functions were not fully understood. In addition, use of different exposure conditions make it difficult to compare the results from different experiments.
2. Characteristics of the response system, i.e., the dependent variable, were not fully understood. In many cases, the underlying mechanism of the response system studied was not known.
3. Dose-response relationship was not established in many instances and conclusions were drawn from a single RFR intensity or exposure duration.

It is well known that the distribution of RFR in an exposed object depends on many factors such as frequency, orientation of exposure, dielectric constant of the tissue, etc. D'Andrea et al. [1987] and McRee and Davis [1984] pointed out the uneven distribution of energy absorbed in the body of an exposed animal with the existence of 'hot spots'. In experiments studying the central nervous system, Williams et al. [1984d] also reported a temperature gradient in the brain of rats exposed to RFR. Structures located in the center of the brain, such as the hypothalamus and medulla, had higher temperatures than peripheral locations, such as the cerebral cortex. In a study by Chou et al. [1985a], comparisons were made of the local SARs in eight brain sites of rats exposed under seven exposure conditions, including exposure in a circular waveguide with the head or tail of an animal facing the radiation source, near field and far field exposures with either E- or H-field parallel to the long-axis of the body, and dorsal exposure in a miniature anechoic chamber with E- or H-field parallel to the long axis of the body. Statistical analysis of the data showed that a) there was a significant difference in local SARs in the eight brain regions measured under each exposure condition, and b) the pattern of energy absorption in different regions of the brain depended on the exposure condition. However, it must be pointed out that in another study [Ward et al., 1986], no temperature 'hot spots' were detected in the brains of rat carcasses and anesthetized rats after irradiation with 2450-MHz RFR. Temperature increases in various regions of the brain were found to be uniform and dependent on the power density of the radiation.

A question that one might ask is whether different absorption patterns in the brain or body could elicit different biological responses in the animal. If this is positive, possible outcomes from the study of bioelectromagnetics research are: (1) a response will be elicited by some exposure conditions and not by others, and (2) different response patterns are elicited by different exposure conditions, even though the average dose rates in the conditions are equal. We [Lai et al., 1984a] reported a difference in responses to the hypothermic effects of pentobarbital depending on whether the rat was exposed with its head facing toward or away from the source of radiation in the waveguide with the average whole body SAR under both conditions remaining the same; however, the patterns of energy absorption in the body and the brain differed in the two exposure conditions. Studies of HACU activity in the different regions of the brain [Lai et al., 1988] also showed that different responses could be triggered using different exposure systems or different waveforms of RFR (continuous-wave or pulsed) with the average whole body SAR held constant under each exposure condition. These data indicate that the energy distribution in the body and other properties of the radiation can be important factors in determining the

outcome of the biological effects of RFR. A series of studies by Frei et al. [1989a,b] also demonstrated some interesting results on this issue. The effects of high intensity 2450- and 2800-MHz RFRs on heart rate, blood pressure, and respiratory rate in ketamine-anesthetized rats were studied. Both frequencies produced increases in heart rate and blood pressure and no significant difference was observed whether continuous-wave or pulsed radiation was used. A difference was observed, however, when the animals were exposed with their bodies parallel to the H- or E-field. In the case of 2450-MHz RFR, the E-orientation exposure produced greater increases in heart rate and blood pressure than the H-orientation exposure; whereas no significant difference in the effects between the two exposure orientations was observed with the 2800-MHz radiation. The authors speculated that the differences could be attributed to the higher subcutaneous temperature and faster rise in colonic temperature in the E-orientation when the rats were exposed at 2450 MHz than at 2800 MHz. Once again, this points out that subtle differences in exposure parameters could lead to different responses. Therefore, due to the peculiar pattern of energy deposition and heating by RFR, it may be impossible to replicate the thermal effect of RFR by general heating, i.e., use of temperature controls.

The fact that dosimetry data were based on stationary models that usually show discrete patterns of energy absorption, further complicate the matter. In animal studies, unless the animal is restrained, the energy absorption pattern changes during the exposure period depending on the position and the orientation of the animal. A possible solution would be to perform long-term exposure experiments, thus, the absorption pattern on the average would be made more uniform.

Another important consideration regarding the biological effects of RFR is the duration or number of exposure episodes. This is demonstrated by the results of some of the studies on the neurological effects of RFR. Depending on the responses studied in the experiments, several outcomes could result: an effect was observed only after prolonged (or repeated) exposure, but not after acute exposure [Baranski, 1972; Baranski and Edelwejn, 1968, 1974; Mitchell et al., 1977; Takashima et al., 1979], an effect disappeared after prolonged exposure suggesting habituation [Johnson et al., 1983; Lai et al., 1987c, 1992a], and different effects were observed after different durations of exposure [Baranski, 1972; Dumanski and Shandala, 1974; Grin, 1974; Lai et al., 1989a, 1989b; Servantie et al., 1974; Snyder, 1971]. All of these different responses reported can be explained as being due to the different characteristics of the dependent variable studied. An interesting question related to this is whether or not intensity and duration of exposure interact, e.g., can exposure to a low intensity over a long duration produce the same effect as exposure to a high intensity radiation for a shorter period?

Thus, even though the pattern or duration of RFR exposure is well-defined, the response of the biological system studied will still be unpredictable if we lack sufficient knowledge of the response system. In most experiments on the neurological effects of RFR, the underlying mechanism of the dependent variable was not fully understood. The purpose of most of the studies was to identify and characterize possible effects of RFR rather than the underlying mechanisms responsible for the effects. This lack of knowledge of the response system studied is not uncommon in biological research. In this regard, it may be appropriate to compare the biological and neurological effects of RFR with those of ethanol. Both entities exert non-specific effects on multiple organs in the body. Their effects are nonspecific, because both ethanol and RFR are not acting on specific receptors. The biological effects of ethanol could be a general action on cell membrane fluidity.

In reviewing the literature on the neurological effects of ethanol, one notices some similarity with those of RFR. In both cases, a wide variety of neurological processes were

reported to be affected after exposure, but without a known mechanism. On the other hand, inconsistent data were commonly found. For example, in the case of the effects of ethanol on dopamine receptors in the brain, an increase [Hruska, 1988; Lai et al., 1980], a decrease [Lucchi et al., 1988; Syvalahti et al., 1988], and no significant change [Muller, 1980; Tabakoff and Hoffman, 1979] in receptor concentration have been reported by different investigators. Such inconsistencies have existed since the late 70's and there has been no satisfactory explanation for them. Similar research findings of increase, decrease, and no significant change in the concentration of muscarinic cholinergic receptors in the cerebral cortex of animals treated with ethanol have also been reported in the literature [Kuriyama and Ohkuma, 1990]. Dosage and route of ethanol treatment, the frequency of administration, and the species of animal studied, etc., could all attribute to variations in the findings [Keane and Leonard, 1989]. As we have discussed earlier, such considerations on the parameters of treatment also apply to the study of the biological effects of RFR. These are further complicated by the special properties of the radiation, such as waveform and modulation. In addition, RFR effects could have rapid onset and offset when the source was turned on and off, whereas the biological effect of ethanol depends on the rates of absorption and metabolism.

Thus, an understanding of the response characteristics of the dependent variables to different parameters of RFR, such as power density, frequency, waveform, etc., is important. Lack of knowledge about such characteristics may explain some of the discrepancies in bioelectromagnetics research results in the literature. Non-linear response characteristics are frequently observed in biological systems, because different mechanisms are involved in producing a response. For example, in the case of apomorphine-induced locomotor activity, a low dose of apomorphine (e.g., 0.1 mg/kg) decreases locomotor activity, whereas a higher dosage (e.g., 1.0 mg/kg) of the drug causes a profound enhancement. A dose in between may cause an insignificant effect. An explanation for this phenomenon is that a low dose of apomorphine activates selectively presynaptic dopamine receptors in the brain, which decreases dopamine release from its terminals and, thus, a decrease in motor activity. At a high dose, apomorphine stimulates the postsynaptic dopamine receptors, leading to an increase in motor activity.

Another common response-characteristic is the inverted-U function. In this situation, a response is only seen at a certain dose range and not at higher or lower dosages. An example of an inverted-U dose-response function is the effect of benzodiazepines on schedule controlled operant behavior. There is not a good explanation for the occurrence of this function. One possible explanation might be that at least two mechanisms, a facilitatory and an inhibitory function, are involved in the response. At a lower dose range of the drug, for example, the facilitatory mechanism predominates and leads to enhancement of the response, whereas, as the dosage increases an inhibitory mechanism is activated, leading to a decline in response. Thus, it is essential that the dose-response function be determined.

The inverted-U response-characteristic can be the basis of some of the 'window' effects reported in bioelectromagnetics research. Thus, with the above considerations, it is not surprising that RFR can cause enhancement, decrement, and no significant effect on a particular response depending upon the exposure conditions. Blackman et al. [1991] stated on the effect of temperature on calcium ion efflux from brain tissue that, "... either outcome (*inhibition or enhancement in release of calcium ions*), or a null result, is possible, depending on the temperature of tissue sample before and during exposure". However, it must be pointed out that

the inverted-U function is not sufficient to account for the 'multiple window' effect reported in one of Blackman's studies [Blackman et al., 1989].

Another important consideration in the study of the central nervous system should be mentioned here. It is well known that the functions of the central nervous system can be affected by activity in the peripheral nervous system. Thirty years ago, McAfee [1961, 1963] pointed out that the thermal effect of RFR on the peripheral nervous system can lead to changes in central nervous system functions and behavior in the exposed animal. This is especially important in the in vivo experiments when the whole body is exposed. However, in most experiments studying the effects of RFR on the central nervous system, the possibility of contribution from the peripheral nervous system was not excluded in the experimental design. Therefore, caution should be taken in concluding that a neurological effect resulted solely from the action of RFR on the central nervous system.

An interesting question arose, whether or not RFR could produce 'non-thermal' biological effects. Many have speculated whether RFR can directly affect the activity of excitable tissues. Schwan [1971, 1977] pointed out that it would take a very high intensity of RFR to directly affect the electrical activity of a cell. On the other hand, Wachtel et al. [1975] have speculated that an RFR-induced polarized current in the membrane of a neuron could lead to changes in activity. Adey [1988] has suggested that cooperative processes in the cell membrane might be reactive to the low energy of oscillating electromagnetic field, leading to a change in membrane potential. Pickard and Barsoum [1988] recorded from cells of the Characeae plant exposed to 0.1-5 MHz pulsed RFR and observed a slow and fast component of change in membrane potential. The slow component was temperature dependent and the fast component was suggested to be produced by rectification of the oscillating electric field induced by RFR on the cell membrane. However, the effect disappeared when the frequency of radiation reached ~10 MHz.

An extreme example of the direct interaction of electromagnetic radiation with a specific biological molecule triggering a neurological effect is the rhodopsin molecules in the rod photorecepter cells that transduce light energy into neural signals. In 1943, a psychophysical experiment by Hecht et al. [1942] suggested that a single photon could activate a rod cell. The molecular biology of rhodopsin is now well understood. It is now known that a single photon can activate a single molecule of rhodopsin. A photon of the visible spectrum turns 11-cis retinol, a moiety of the rhodopsin molecule, to an all-trans form. This triggers a cascade of molecular activities involving specific G-protein, the conversion of cyclic-GMP to 5'-GMP, and eventually closing the sodium-ion channels on the cell membrane of the rod cell. This cascade action leads to a powerful amplification of the photon signal. It was estimated that one photon can affect several hundred C-GMP molecules. Such change is enough to hyperpolarize a rod cell and lead to signal transmission through its synapse [Liebman et al., 1987; Stryer, 1987]. Can a similar molecular sensitive to RFR exist? The problem is that RFR energy is several orders of magnitude ($\sim 10^6$) lower than that of a photon at the visual spectrum. It is difficult to visualize a similar molecular mechanism sensitive enough to detect RFR.

Another consideration is that the ambient level of RFR is very low in the natural environment and could not have generated enough selection pressure for the evolutionary development of such a molecular mechanism. On the other hand, there may be some reason for the development of a molecular mechanism for the detection of static or low frequency electric or magnetic fields. An example is the electroreception mechanism of two Australian monotremes, the platypus, *Ornithorhynchus anatinus*, and the echidna, *Tachyglossus aculeatus* [Gregory et al.,

1989a,b; Iggo et al., 1992; Scheich et al., 1986]. Apparently, receptors sensitive to low-level electric fields exist in the snout and bill of these animals, respectively. Electrophysiological recordings from the platypus show that receptors in the bill can be sensitive to a static or sinusoidally changing (12-300 Hz) electric field of 4-20 mV/cm, and cells in the cerebral cortex can respond to a threshold field of 300 μV/cm. Moreover, behavioral experiments showed that the platypus can detect electric fields as small as 50 μV/cm. In the echidna snout, receptors can respond to fields of 1.8-73 mV/cm. These neural mechanisms enable the animals to detect muscular movements of their prey, termites and shrimps. It would be interesting to understand the transduction mechanism in the electroreceptors in these animals. However, it remains to be seen whether RFR can generate a static or ELF field in tissue and that a similar electroreceptor mechanism exists in other mammals.

Another possible explanation suggested for the neurological effects of RFR is stress. This hypothesis has been proposed by Justesen et al. [1973] and Lu et al. [1980] and based on high intensity of exposure. We have also proposed recently that low-level RFR may be a 'stressor' [Lai et al., 1987a]. Our speculation is based on the similarity of the neurological effects of known stressors (e.g., body-restraint, extreme ambient temperature) and those of RFR (see Table 1 in Lai et al., 1987a). Our recent experiments suggesting that low-level RFR activates both endogenous opioids and corticotropin-releasing factor in the brain further support this hypothesis. Both neurochemicals are known to play important roles in an animal's responses to stressors [Amir et al., 1980; Fisher, 1989]. However, it is difficult to prove that an entity is a stressor, since the criteria of stress are not well defined and the caveat of stress is so generalized that it has little predictive power on an animal's response.

In conclusion, I believe the questions on the biological effects of RFR and the discrepancies in research results in the literature can be resolved by (a) a careful and thorough examination of the effects of the different radiation parameters, and (b) a better understanding of the underlying mechanisms involved in the responses studied. With these considerations, it is very unlikely that the neurological effects of RFR can be accounted for by a single unifying neural mechanism.

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REFERENCES

Adair, E.R., 1983, "Microwaves and Thermoregulation," Academic Press, New York, NY.

Adey, W.R., 1988, The cellular microenvironment and signalling through cell membrane, *in*: "Electromagnetic fields and Neurobehavioral Functions," M.E. O'Connor and R.H. Lovely, eds., *Prog Clin Biol Res* 257:265-288.

Adey, W.R., Bawin, S.M. and Lawrence, A.F., 1982, Effects of weak amplitude-modulated microwave fields on calcium efflux from awake cat cerebral cortex, *Bioelectromagnetics* 3:295-307.

Akyel, Y., Hunt, E.L., Gambrill, C., Varga, Jr. C., 1991, Immediate postexposure effects of high-peak-power microwave pulses on operant behavior of Wistar rats, *Bioelectromagnetics* 12:183-195.

Albert, E.N., 1977, Light and electron microscopic observations on the blood-brain barrier after microwave irradiation, *in*: "Symposium on Biological Effects and Measurement of Radio Frequency Microwaves," D.G. Hazzard, ed., HEW Publication (FDA) 77-8026, Rockville, MD.

Albert, E.N., 1979a, Reversibility of microwave induced blood-brain barrier permeability, *Radio Sci* 14:323-327.

Albert, E.N., 1979b, Current status of microwave effects on the blood-brain barrier, *J Microwave Power* 14:281-285.

Albert, E.N., and DeSantis, M., 1975, Do microwaves alter nervous system structure? *Ann NY Acad Sci* 247:87-108.

Albert, E.N., and DeSantis, M., 1976, Histological observations on central nervous system, *in*: "Biological Effects of Electromagnetic Waves," vol. 1, C.C. Johnson and M.C. Shore, eds., HEW Publication (FDA) 77-8010, Rockville, MD.

Albert, E.N., and Kerns, J.M., 1981, Reversible microwave effects on the blood-brain barrier, *Brain Res* 230:153-164.

Albert, E.N., and Sherif, M., 1988, Morphological changes in cerebellum of neonatal rats exposed to 2.45 GHz microwaves, *in*: "Electromagnetic Fields and Neurobehavioral Functions," M.E. O'Connor and R.H. Lovely, eds., *Prog Clin Biol Res* 257: 135-151.

Albert, E.N., Sherif, M.F., and Papadopoulos, N-J., 1981a, Effects of non-ionizing radiation on the Purkinje cells of the uvula in squirrel monkey cerebellum, *Bioelectromagnetics* 2:241-246.

Albert, E.N., Sherif, M.F., Papadopoulos, N.J., Slaby, F.J., and Monahan, J., 1981b, Effect of nonionizing radiation on the Purkinje cells of the rat cerebellum, *Bioelectromagnetics* 2:247-257.

Altman, J., 1975, Effects of interference with cerebellar maturation on the development of locomotion: an experimental model of neurobehavioral retardation, *in*: "Brain Mechanisms in Mental Retardation," N.A. Buchwald and M.A.B. Brazier, eds., Academic Press, New York, NY.

Amir, S., Brown, Z.W., and Amit, Z., 1980, The role of endorphins in stress: evidence and speculations, *Neurosci Biobehav Rev* 4:77-86.

Arber, S.L., and Lin, J.C., 1985, Microwave-induced changes in nerve cells: effects of modulation and temperature, *Bioelectromagnetics* 6:257-270.

Ashani, Y., Henry, F.H., and Catravas, G.N., 1980, Combined effects of anticholinesterase drugs and low-level microwave radiation, *Radiat Res* 84:469-503.

Atweh, S., Simon, J.R., and Kuhar, M.J., 1975, Utilization of the sodium-dependent high-affinity choline uptake in vitro as a measure of activity of cholinergic neurons in vivo, *Life Sci* 17:1534-1544.

Baranski, S., 1972, Histological and histochemical effects of microwave irradiation on the central nervous system of rabbits and guinea pigs, *Am J Physiol Med* 51:182-190.

Baranski, S., and Edelwejn, Z., 1968, Studies on the combined effects of microwaves and some drugs on bioelectric activity of the rabbit central nervous system, *Acta Physiol Polon*, 19:37-50.

Baranski, S., and Edelwejn, Z., 1974, Pharmacological analysis of microwave effects on the central nervous system in experimental animals, *in*: "Biological Effects and Health Hazards of Microwave Radiation: Proceedings of an International Symposium," P. Czerski, et al., eds., Polish Medical Publishers, Warsaw.

Bawin, S.M., Gavalas-Medici, R.J., and Adey, W.R., 1973, Effects of modulated very high frequency fields on specific brain rhythms in cats, *Brain Res* 58:365-384.

Bawin, S.M., Kaczmarek, L.K., and Adey, W.R., 1975, Effects of modulated VHF fields on the central nervous system, *Annals NY Acad Sci* 247:74-81.

Bawin, S.M., Adey, W.R., and Sabbot, I.M., 1978, Ionic factors in release of $^{45}Ca^{2+}$ from chicken cerebral tissue by electromagnetic fields, *Proc Nat'l Acad Sci USA* 75:6314-6318.

Benson, E.B., Lange, D.G., Fujimoto, J.M., and Ishi, T.K., 1983, Effects of acute microwave irradiation on phenobarbital sleep and disposition to brain in mice, *J Toxicol Environ Health* 11:261-274.

Bermant, R.I., Reeves, D.L., Levinson, D.M., and Justesen, D.R., 1979, Classical conditioning of microwave-induced hyperthermia in rat, *Radio Sci* 14(6):201-207.

Blackman, C.F., Elder, J.A., Weil, C.M., Benane, S.G., Eichinger, D.C., and House, D.E., 1979, Induction of calcium-ion efflux from brain tissue by radio-frequency radiation: effects of modulation frequency and field strength, *Radio Sci* 14:93-98.

Blackman, C.F., Benane, S.G., Elder, J.A., House, D.E., Lampe, J.A., and Faulk, J.M., 1980a, Induction of calcium ion efflux from brain tissue by radiofrequency radiation: effect of sample number and modulation frequency on the power-density window, *Bioelectromagnetics* 1:35-43.

Blackman, C.F., Benane, S.G., Joines, W.T., Hollis, M.A., and House, D. E., 1980b, Calcium ion efflux from brain tissue: power density versus internal field-intensity dependencies at 50-MHz RF radiation, *Bioelectromagnetics* 1:277-283.

Blackman, C.F., Benane, S.G., House, D.E., and Joines, W.T., 1985, Effects of ELF (1-120 Hz) and modulated (50 Hz) RF field on the efflux of calcium ions from brain tissue, in vitro, *Bioelectromagnetics* 6:1-11.

Blackman, C.F., Benane, S.G., Elliot, D.J., House, D.E., and Pollock, M.M., 1988, Influence of electromagnetic fields on the efflux of calcium ions from brain tissue, in vivo: a three-model analysis consistent with the frequency response up to 510 Hz, *Bioelectromagnetics* 9:215-227.

Blackman, C.F., Kinney, L.S., House, D.E., and Joines, W.T., 1989, Multiple power density windows and their possible origin, *Bioelectromagnetics* 10:115-128.

Blackman, C.F., Benane, S.G., and House, D.E., 1991, The influence of temperature during electric and magnetic-field induced alteration of calcium-ion release from in vitro brain tissue, *Bioelectromagnetics* 12:173-182.

Blackwell, R.P., 1980, Effects of microwave exposure on anesthesia in the mouse, *in*: "Proceeding on the International Symposium on the Biological Effects of Electromagnetic Waves," UNSI, CNFRS, Jouy en Josas, France.

Blasberg, R.G., 1979, Problems of quantifying effects of microwave irradiation on the blood-brain barrier, *Radio Sci* 14(6):335-344.

Bolwig, T.G., 1988, Blood-brain barrier studies with special reference to epileptic seizure, *Acta Psychiatr Scand* 78(345):15-20.

Braestrup, C., and Squires, R.F. , 1978, Pharmacological characterization of benzodiazepine receptors in the brain, *Eur J Pharmac* 48:263-270.

Braestrup, C., Neilsen, M., Neilsen, E.B., and Lyon, M., 1979, Benzodiazepine receptors in the brain as affected by different experimental stresses: the changes are small and not unidirectional, *Psychopharmacology* 65:273-277.

Bruce-Wolfe, V., and Justesen, D.R., 1985, Microwaves retard the anesthetic action of pentobarbital, *Abstr Ann Meeting Bioelectromagnetics Soc* 7:47.

Carroll, D.R., Levinson, D.M., Justesen, D.R., and Clarke, R.L., 1980, Failure of rats to escape from a potentially lethal microwave field, *Bioelectromagnetics* 1:101:115.

Catravas, C.N., Katz, J.B., Takenaga, J., and Abbott, J.R., 1976, Biochemical changes in the brain of rats exposed to microwaves of low power density (symposium summary), *J Microwave Power* 11:147-148.

Chamness, A.F., Scholes, H.R., Sexauer, S.W., and Frazer, J.W., 1976, Metal ion content of specific areas of the rat brain after 1600-MHz radiofrequency irradiation, *J Microwave power* 11:333-337.

Chang, B.K., Huang, A.T., Joines, W.T., and Kramer, R.S., 1982, The effect of microwave radiation (1.0 GHz) on the blood-brain barrier, *Radio Sci* 17:165-168.

Chizhenkova, R.A., 1988, Slow potentials and spike unit activity of the cerebral cortex of rabbits exposed to microwaves, *Bioelectromagnetics* 9:337-345.

Chou, C.K. and Galambos, S.R., 1979, Middle ear structures contribute little to auditory perception of microwaves, *J Microwave Power* 14:321-326.

Chou, C.K. and Guy, A.W., 1978, Effects of electromagnetic fields on isolated nerve and muscle preparation, *IEEE Trans Microwave Th Tech* MTT-26:141-147.

Chou, C.K., and Guy, A.W., 1979a, Carbon-loaded Teflon electrodes for chronic EEG recordings in microwave research, *J Microwave Power* 14:399-404.

Chou, C.K. and Guy, A.W., 1979b, Microwave-induced auditory responses in guinea pigs: relationship of threshold and microwave-pulse duration, *Radio Sci* 14(6):193-197.

Chou, C.K., Galambos, R., Guy, A.W., and Lovely, R.H., 1975, Cochlear microphonics generated by microwave pulses, *J Microwave Power* 10:361-367.

Chou, C.K., Guy, A.W., and Galambos, R., 1982a, Auditory perception of radiofrequency electromagnetic fields, *J Acoust Soc Am* 71:1321-1334.

Chou, C.K., Guy, A.W., McDougall, J.B., and Han, L.F., 1982b, Effects of continuous and pulsed chronic microwave exposure on rabbits, *Radio Sci* 17:185-193.

Chou, C.K., Guy, A.W., and Johnson, R.B., 1984, SAR in rats exposed in 2450-MHz circularly polarized waveguide, *Bioelectromagnetics* 5:389-398.

Chou, C.K., Guy, A.W., McDougall, J., and Lai, H., 1985a, Specific absorption rate in rats exposed to 2450-MHz microwaves under seven exposure conditions, *Bioelectromagnetics* 6:73-88.

Chou, C.K., Yee, K.C., and Guy, A.W., 1985b, Auditory response in rats exposed to 2450-MHz electromagnetic fields in a circularly polarized waveguide, *Bioelectromagnetics* 6:323-326.

Cotman, C.W., Brinton, R.E., Jalaburda, A., McEwen, B., and Schneider, D.M., eds., 1987, "The Neuro-Immune-Endocrine Connection," Raven Press, New York, NY.

Cunningham, C.L., Crabbe, J.C., and Rigter, H., 1984, Pavlovian conditioning of drug-induced changes in body temperature, *Pharmac Ther* 23:365-391.

Czerski, P., Ostrowski, K., Shore, M.L., Silverman, C.H., Sues, M.J., and Waldeskog, B., eds., 1974, "Biological Effects and Health Hazard of Microwave Radiation: Proceedings of an International Symposium," P. Czerski, et al., eds., Polish Medical Publisher, Warsaw.

D'Andrea, J.A., Gandhi, O.P., and Kesner, R.P., 1976, Behavioral effects of resonant electromagnetic power absorption in rats, *in*: "Biological Effects of Electromagnetic Waves," vol 1, C.C. Johnson and M.L. Shore, eds., HEW Publication (FDA) 77-8010, Rockville, MD.

D'Andrea, J.A., Gandhi, O.P., and Lords J.L., 1977, Behavioral and thermal effects of microwave radiation at resonant and nonresonant wavelengths, *Radio Sci* 12:251-256.

D'Andrea, J.A., Gandhi, O.P., Lords, J.L., Durney, C.H., Johnson, C.C., and Astle, L., 1979, Physiological and behavioral effects of chronic exposure to 2450-MHz microwaves, *J Microwave Power* 14:351-362.

D'Andrea, J.A., Gandhi, O.P., Lords. J.L., Durney, C.H., Astle, L., Stensaas, L.J., and Schoenberg, A.A., 1980, Physiological and behavioral effects of prolonged exposure to 915 MHz microwaves, *J Microwave Power* 15(2):123-135.

D'Andrea, J.A., DeWitt, J.R., Gandhi, O. P., Stensaas, S., Lords, J.L., and Nielson, H.C., 1986a, Behavioral and physiological effects of chronic 2450-MHz microwave irradiation of the rat at 0.5 mW/cm^2, *Bioelectromagnetics* 7:45-56.

D'Andrea, J.A., DeWitt, J.R., Emmerson, R.Y., Bailey, C., Stensaas, S., and Gandhi, O. P., 1986b, Intermittent exposure of rat to 2450-MHz microwaves at 2.5 mW/cm^2: behavioral and physiological effects, *Bioelectromagnetics* 7:315-328.

D'Andrea, J.A., Emmerson, R.Y., Dewitt, J.R., and Gandhi, O.P., 1987, Absorption of microwave radiation by the anesthetized rat: electromagnetic and thermal hotspots in body and tail, *Bioelectromagnetics* 8:385-396.

D'Andrea, J.A., Cobb, B.L., and de Lorge, J., 1989, Lack of behavioral effects in the rhesus monkey to high peak power microwave pulses at 1.3 GHz, *Bioelectromagnetics* 10:65-76.

da Silva, F.L., 1991, EEG analysis: theory and practice, *in*: "Electroencephalography: Basic Principles, Clinical Applications, and Related Fields," E. Niedermeyer and F.L. da Silva, eds., Urban and Schwargenberg, Baltimore, MD.

Dekker, A.J.A.M., Conner, D.J., and Thal, L.J., 1991, The role of cholinergic projections from the nucleus basalis in memory, *Neurosci Biobehav Rev* 15:299-317.

de Lorge, J.O., 1976, The effects of microwave radiation on behavior and temperature in rhesus monkeys, *in*: "Biological Effects of Electromagnetic Waves," vol. 1, C.C. Johnson and M.L. Shore, eds., HEW Publication (FDA) 77-8010, Rockville, MD.

de Lorge, J.O., 1979, Operant behavior and rectal temperature of squirrel monkeys during 2.45-GHz microwave irradiation, *Radio Sci* 14(6):217-225.

de Lorge, J.O., 1985, Effects of microwaves on schedule-controlled behavior, *in*: "Behavioral Effects of Microwave Radiation Absorption," J.C. Monahan, and J.A. D'Andrea, eds., HHS Publication, FDA 85-8238, U.S. Government Printing Office, Washington, DC.

de Lorge, J., and Ezell, C.S., 1980, Observing-responses of rats exposed to 1.28- and 5.62-GHz microwaves, *Bioelectromagnetics* 1:183-198.

D'Inzeo, G., Bernardi, P., Eusebi, F., Grassi, F., Tamburello, C., and Zani, B.M., 1988, Microwave effects on acetylcholine-induced channels in cultured chick myotubes, *Bioelectromagnetics* 9:363-372.

Dumansky, J.D., and Shandala, M.G., 1974, The biologic action and hygienic significance of electromagnetic fields of super high and ultra high frequencies in densely populated areas, *in*: "Biologic Effects and Health Hazard of Microwave Radiation: Proceedings of an International Symposium," P. Czerski, et al., eds., Polish Medical Publishers, Warsaw.

Dunn, A.J., 1989, Psychoneuroimmunology for the psychoneuroendocrinologist: a review of animal studies of nervous system-immune system interactions, *Psychoneuroendocrinology* 14:251-274.

Dutta, S.K., Subramoniam, A., Ghosh, B., and Parshad, R., 1984, Microwave radiation-induced calcium ion efflux from human neuroblastoma cells in culture, *Bioelectromagnetics* 5:71-78.

Dutta, S.K., Ghosh, B., and Blackman, C.F., 1989, Radiofrequency radiation-induced calcium ion efflux enhancement from human and other neuroblastoma cells in culture, *Bioelectromagnetics* 10:197-202.

Dutta, S.K., Das, K., Ghosh, B., and Blackman, C.F., 1992, Dose dependence of acetylcholinesterase activity in neuroblastoma cells exposed to modulated radio-frequency electromagnetic radiation, *Bioelectromagnetics* (In press).

Eikelboom, R., and Stewart, J., 1982, Conditioning of drug-induced physiological responses, *Psychol Rev* 89:507-528.

Estevez, E.E., Jernsalinsky, D., Medina, J.H., and DeRobertis, E., 1984, Cholinergic muscarinic receptors in rat cerebral cortex, basal ganglia, and cerebellum undergo rapid and reversible changes after acute stress, *Neurosci* 13:1353-1357.

Finkelstein, Y., Koffler, B., Rabey, J.M., and Gilad, G.M., 1985, Dynamics of cholinergic synaptic mechanisms in rat hippocampus after stress, *Brain Res* 343:314-319.

Fisher, L.A., 1989, Corticotropin-releasing factor: endocrine and automatic integration of responses to stress, *Trends Pharmac Sci* 10:189-193.

Frei, M.R., Jauchem, J.R., Padilla, J.M., and Merritt, J.H., 1989a, Thermal and physiological responses of rats exposed to 2.45-GHz radiofrequency radiation: a comparison of E and H orientations, *Radiat Envir Biophys* 28:235-246.

Frei, M.R., Jauchem, J.R., and Padilla, J.M., 1989b, Thermal and physiological changes in rats exposed to CW and pulsed 2.8 GHz radiofrequency radiation in E and H orientations, *Int J Radiat Biol* 56:1033-1044.

Frey, A.H., 1961, Auditory system response to radio frequency energy, *Aerospace Med* 32:1140-1142.

Frey, A.H., 1977, Behavioral effects of electromagnetic energy, *in*: "Symposium on Biological Effects and Measurement of Radio Frequency Microwaves," D.J. Hazzard, ed., HEW Publication (FDA), 77-8026, Rockville, MD.

Frey, A.H., and Feld, S.R., 1975, Avoidance by rats of illumination with low power nonionizing electromagnetic energy, *J Comp Physiol Psychol* 89:183-188.

Frey, A.H., and Wesler, L.S., 1983, Dopamine receptors and microwave energy exposure, *J Bioelectr* 2:145-157.

Frey, A.H., Feld, S.R., and Frey, B., 1975, Neural function and behavior: defining the relationship. *Ann N Y Acad Sci* 247:433-439.

Gage, M.I., 1979a, Microwave irradiation and ambient temperature interact to alter rat behavior following overnight exposure, *J Microwave Power* 14:389-398.

Gage, M.I., 1979b, Behavior in rats after exposure to various power densities of 2450 MHz microwaves, *Neurobehav Toxicol* 1:137-143.

Galloway, W.D., 1975, Microwave dose-response relationship on two behavioral tasks, *Ann N Y Acad Sci* 247:410-416.

Galloway, W.D., and Waxler, M., 1977, Interaction between microwaves and neuroactive compounds, *in*: "Symposium on Biological Effects and Measurement of Radio Frequency Microwaves," D.J. Hazzard, ed., HEW Publication (FDA) 77-8026, Rockville, MD.

Galvin, M.J., Parks, D.L., and McRee, D.L., 1981, Influence of 2.45 GHz microwave radiation on enzyme activity, *Radiat Environ Biophys* 19:149-156.

Galvin, M.J., Tilson, H.A., Mitchell, C.L., Peterson, J., and McRee, D.I., 1986, Influence of pre- and postnatal-exposure of rats to 2.45-GHz microwave radiation on neurobehavioral functions, *Bioelectromagnetics* 7:57-71.

Gandhi, C.R., and Ross, D.H., 1989, Microwave induced stimulation of ^{32} Pi- incorporation into phosphoinositides of rat brain synaptosomes, *Radiat Environ Biophys* 28:223-234.

Gandhi, V.C., and Ross, D.H., 1987, Alteration in a-adrenergic and muscarinic cholinergic receptor binding in rat brain following nonionizing radiation, *Radiat Res* 109:90-99.

Garcia, J., and Koelling, R., 1966, Relation of cue to consequence in avoidance learning, *Psychonom Sci* 4:123-124.

Garcia, J., Ervin, F., and Koelling, R., 1966, Learning with prolonged delay of reinforcement, *Psychonom Sci* 5:121-122.

Goldman, H., Lin, J.C., Murphy, S., and Lin, M.F., 1984, Cerebrovascular permeability to Rb-86 in the rat after exposure to pulsed microwaves, *Bioelectromagnetics* 5:323-330.

Goldstein, L., and Sisko, Z., 1974, A quantitative electro-encephalographic study of the acute effect of X-band microwaves in rabbits, *in*: "Biological Effects and Health Hazards of Microwave Radiation: Proceedings of an International Symposium," P. Czerski, et al., eds., Polish Medical Publishers, Warsaw.

Gordon, Z.V., 1970, Biological effects of microwaves in occupational hygiene, Israel Program for Scientific Translations, Jerusalem, Israel, NASA77F-633, TT70-50087:NTIS N71-14632.

Gregory, J.E., Iggo, A., McIntyre, A.K. and Proske, U., 1989a, Responses of electroreceptors in the platypus bill to steady and alternating potentials, *J Physiol* 408:391-404.

Gregory, J.E., Iggo, A., McIntyre, A.K. and Proske, U., 1989b, Response of electro-receptors in the snout of the echidna, *J Physiol* 414:521-538.

Grin, A.N., 1974, Effects of microwaves on catecholamine metabolism in brain, *US Joint Pub Research Device Rep* JPRS 72606.

Gruenau, S.P., Oscar, K.J., Folker, M.T., and Rapoport, S.I.,1982, Absence of microwave effect on blood-brain barrier permeability to ^{14}C-sucrose in the conscious rat, *Exp Neurobiol* 75:299-307.

Guy, A.W., 1979, Miniature anechoic chamber for chronic exposure of small animals to plane wave microwave field, *J Microwave Power* 14:327-338.

Guy, A.W., Chou, C.K., Lin, J.C., and Christensen, D., 1975, Microwave-induced acoustic effects in mammalian auditory systems and physical materials, *Ann NY Acad Sci* 247:194-215.

Guy, A.W., Wallace, J., and McDougall, J.A., 1979, Circularly polarized 2450-MHz waveguide system for chronic exposure of small animals to microwaves, *Radio Sci* 14(6):63-74.

Hecht, S., Schlaer, S., and Pirene, M.H., 1942, Energy, quanta, and vision, *J Gen Physiol* 25:819-840.

Hjeresen, D.L., Doctor, S.R., and Sheldon, R.L., 1979, Shuttlebox-side preference as mediated by pulsed microwaves and conventional auditory cue, *in*: "Electromagnetic Fields in Biological System," S.S.Stuchly, ed., Ottawa, Canada.

Hjeresen, D.L., Umbarger, K.O., and McElroy, J.F., 1987, Benzodiazepine receptor antagonist RO 15-1788 blocks the 2.45 GHz microwave attenuation of ethanol-induced hypothermia, *Abst Ann Meeting Bioelectromagnetics Soc* 9:25.

Hjeresen, D.L., Francendese, A., and O'Donnell, J.M., 1988, Microwave attenuation of ethanol-induced hypothermia: ethanol tolerance, time cause, exposure duration and dose response studies, *Bioelectromagnetics* 9:63-78.

Hjeresen, D.L., Francendese, A., and O'Donnell, J.M., 1989, Microwave attenuation of ethanol-induced interactions with noradrenergic neurotransmitter systems, *Health Phys* 56:767-776.

Hruska, R.E., 1988, Effect of ethanol administration on striatal D_1 and D_2 dopamine receptors, *J Neurochem* 50:1929-1933.

Hunt, E.L., King, N.W., and Phillips, R.D., 1975, Behavioral effects of pulsed microwave radiation, *Ann NY Acad Sci* 247:440-453.

Iggo, A., Gregory, J.E., and Proske, U., 1992, The central projection of electrosensory information in the platypus, *J Physiol* 447:449-465.

Jauchem, J.R., 1985, Effects of drugs on thermal responses to microwaves, *Gen Pharmacol* 16:307-310.

Jauchem, J.R., Frei, M.R., and Heinmets, F., 1983, Thermal bradycardia during radiofrequency radiation, *Physiol Chem Phys* 15:429-434.

Jauchem, J.R., Frei, M.R., and Heinmets, F., 1984, Increased susceptibility to radiofrequency radiation due to pharmacological agents, *Aviat Space Environ Med* 55:1036-1040.

Jauchem, J.R., Frei, M.R., and Heinmets, F., 1985, Effects of psychotropic drugs on thermal responses to radiofrequency radiation, *Aviat Space Environ Med* 56:1183-1188.

Jenkins, H.M., 1970, Sequential organization on schedules of reinforcement, *in*: "The Theory of Reinforcement Schedules," W.N. Schoenfeld, ed., Appleton-Century-Crofts, New York, NY.

Johnson, C.C., and Guy, A.W., 1972, Nonionizing electromagnetic wave effect in biological materials and systems, *Proc IEEE* 60:692-718.

Johnson, R.B., Meyers, D.E., Guy, A.W., Lovely, R.H., and Galambos, R., 1976, Discriminative control of appetitive behavior by pulsed microwave radiation in rats, *in*: "Biological Effects of Electromagnetic Waves," vol. 1, C.C. Johnson and M.L. Shore, eds., HEW Publication (FDA) 77-88010, Rockville, MD.

Johnson, R.B., Hamilton, J., Chou, C.K., and Guy, A.W., 1980, Pulsed microwave reduction of diazepam-induced sleeping in the rat, *Abst Ann Meeting Bioelectromagnetrics Soc* 2:4.

Johnson, R.B., Spackman, D., Crowley, J., Thompson, D., Chou, C.K., Kunz, L.L., and Guy, A.W., 1983, Effects of long-term low-level radiofrequency radiation exposure on rats, vol. 4, Open field behavior and corticosterone, USAF SAM-TR83-42, Report of USAF School of Aerospace Medicine, Brooks AFB, San Antonio, TX.

Justesen, D.R., 1980, Microwave irradiation and blood-brain barrier, *Proc IEEE* 68:60-67.

Justesen, D.R., Levinson, D.M., and Justesen, L.R., 1973, Psychogenic stressors are potent mediators of the thermal response to microwave irradiation, *in*: "Biological Effects and Health Hazards of Microwave Radiation: Proceedings of an International Symposium," P. Czerski, et al., eds., Polish Medical Publishers, Warsaw.

Kaplan, J., Polson, R., Rebert, C., Lunan, K., and Gage, M., 1982, Biological and behavioral effect of pre- and post-natal exposure to 2450 MHz electromagnetic radiation in the squirrel monkey, *Radio Sci* 171(5):135-144.

Katoh, A., Nabeshima, T., and Kameyama, T., 1990, Behavioral changes induced by stressful situation: effects of enkephalins, dynorphin, and their interaction, *J. Pharmac Exp Ther* 253:600-607.

Keane, B., and Leonard, B.E., 1989, Rodent models of alcoholism: a review, *Alcohol Alcoholism* 24:299-309.

King, N.W., Justesen, D.R., and Clarke, R.L., 1971, Behavioral sensitivity to microwave irradiation, *Science* 172:398-401.

Kues, H.A., and Monahan, J.C., 1992, Microwave-induced changes to the primate eye, *Johns Hopkins APL Tech Digest* 13:244-254.

Kues, H.A., McLeod, D.S., Monahan, J.C., D'Anna, S.A., and Lutty, G.S., 1990, Retinal changes in the primate following pulsed 2.45-GHz exposures, *Abst Ann Meeting Bioelectromagnetics Soc* 12:22.

Kues, H.A., Monahan, J.C., D'Anna, S.A., McLeod, D.S., Lutty, G.A., and Koslov, S., 1992, Increased sensitivity of the non-human primate eye to microwave radiation following ophthalmic drug pretreatment, *Bioelectromagnetics* (In press).

Kuriyama, K., and Ohkuma, S., 1990, Alteration in the function of cerebral neurotransmitter receptors during the establishment of alcohol dependence: neurochemical aspects, *Alcohol Alcoholism* 25:239-249.

Lai, H., 1987, Acute exposure to noise affects sodium-dependent high-affinity choline uptake in the central nervous system of the rat, *Pharmac Biochem Behav* 28:147-151.

Lai, H., 1992, Research on the neurological effects of nonionizing radiation at the University of Washington, *Bioelectromagnetics* 13:513-526.

Lai, H., and Carino, M.A., 1990a, Effects of noise on high-affinity choline uptake in the frontal cortex and hippocampus of the rat are blocked by intracerebroventricular injection of corticotropin-releasing factor antagonist, *Brain Res* 527:354-358.

Lai, H., and Carino, M.A., 1990b, Acute white noise exposure affects the concentration of benzodiazepine receptors in the brain of the rat, *Pharmacol Biochem Behav* 36:985-987.

Lai, H., Carino, M.A., and Horita, A., 1980, Effects of ethanol on central dopamine functions, *Life Sci* 27:299-304.

Lai, H., Horita, A., Chou, C.K., and Guy, A.W., 1983, Psychoactive drug response is affected by acute low-level microwave irradiation, *Bioelectromagnetics* 4:205-214.

Lai, H., Horita, A., Chou, C.K., and Guy, A.W., 1984a, Acute low-level microwave irradiation and the actions of pentobarbital: effects of exposure orientation, *Bioelectromagnetics* 5:203-212.

Lai, H., Horita, A., Chou, C.K., and Guy, A.W., 1984b, Low-level microwave irradiation affects ethanol-induced hypothermia and ethanol consumption, *Bioelectromagnetics* 5:213-220.

Lai, H., Horita, A., Chou, C.K., and Guy, A.W., 1984c, Microwave-induced postexposure hyperthermia: involvement of endogenous opioids and serotonin, *IEEE Trans Microwave Th Tech* MTT-32:882-886.

Lai, H., Horita, A., Chou, C.K., and Guy, A.W., 1986a., Low-level microwave irradiation attenuates naloxone-induced withdrawal syndrome in morphine-dependent rats, *Pharmac Biochem Behav* 24:151-153.

Lai, H., Horita, A., Chou, C.K., and Guy, A.W., 1986b, Effects of low-level microwave irradiation on amphetamine hyperthermia are blockable by naloxone and classically conditionable, *Psychopharmacology* 88:354-361.

Lai, H., Zabawska, J., and Horita, A., 1986c, Sodium-dependent, high-affinity choline uptake in hippocampus and frontal cortex of the rat affected by acute restraint stress, *Brain Res* 372:366-369.

Lai, H., Horita, A., Chou, C.K., and Guy, A.W., 1987a, A review of microwave irradiation and actions of psychoactive drugs, *IEEE Eng Med Biol* 6(1):31-36.

Lai, H., Horita, A., Chou, C.K., and Guy, A.W., 1987b, Low-level microwave irradiation affects central cholinergic activity in the rat, *J Neurochem* 48:40-45.

Lai, H., Horita, A., Chou, C.K., and Guy, A.W., 1987c, Effects of low-level microwave irradiation on hippocampal and frontal cortical choline uptake are classically conditionable, *Pharmac Biochem Behav* 27:635-639.

Lai, H., Horita, A., and Guy, A.W., 1988, Acute low-level microwave exposure and central cholinergic activity: studies on irradiation parameters, *Bioelectromagnetics*, 9:355-362.

Lai, H., Carino, M.A., Horita, A., and Guy, A.W., 1989a, Acute low-level microwave exposure and central cholinergic activity: a dose-response study, *Bioelectromagnetics*, 10:203-209.

Lai, H., Carino, M.A., and Guy, A.W., 1989b, Low-level microwave irradiation and central cholinergic systems, *Pharmac Biochem Behav* 33:131-138.

Lai, H., Carino, M.A., Horita, A., and Guy, A.W., 1990, Corticotropin-releasing factor antagonist blocks microwave-induced changes in central cholinergic activity in the rat, *Brain Res Bull* 25:609-612.

Lai, H., Carino, M.A., Wen, Y.F., Horita, A., and Guy, A.W., 1991, Naltrexone pretreatment blocks microwave-induced changes in central cholinergic receptors, *Bioelectromagnetics* 12:27-33.

Lai, H., Carino, M.A., Horita, A., and Guy, A.W., 1992a, Single vs repeated microwave exposure: effects on benzodiazepine receptors in the brain of the rat, *Bioelectromagnetics* 13:57-66.

Lai, H., Carino, M.A., Horita, A., and Guy, A.W., 1992b, Opioid receptor subtypes mediating the microwave-induced decreases in central cholinergic activity in the rat, *Bioelectromagnetics* 13:237-247.

Lai, H., Horita, A., and Guy, A.W., 1993, Microwave irradiation affects radial-arm maze performance in the rat, *Bioelectromagnetics* (In press).

Lange, D.G., and Sedmak, J., 1991, Japanese encephalitis virus (JEV): potentiation of lethality in mice by microwave radiation, *Bioelectromagnetics* 12:335-348.

Le, A.D., Poulos, C.K., and Cappell, H., 1979, Conditioned tolerance to the hypothermic effect of ethyl alcohol, *Science* 206:1109-1110.

Lebovitz, R.M., 1980, Behavioral changes during long-term microwave irradiation, *in*: "Proceeding of the International Symposium on the Biological Effects of Electromagnetic waves," UNSI, CNFRS, Jouy-en-Josas, France.

Lebovitz, R.M., and Seaman, R.L., 1977a, Microwave hearing: the responses of single auditory neurons in the cat to pulsed microwave radiation, *Radio Sci* 12(6):229-236.

Lebovitz, R.M., and Seaman, R.L., 1977b, Single auditory unit responses to weak, pulsed microwave radiation, *Brain Res* 126:370-375.

Levin, E.D., 1988, Psychopharmacological effects in the radial-arm maze, *Neurosci Biobehav Rev* 12:169-175.

Levinson, D.M., Grove, A.M., Clarke, L.R., and Justesen, D.R., 1982, Photic cuing of escape by rats from an intense microwave field, *Bioelectromagnetics* 3:105-116.

Liebman, P.A., Parker, K.R., and Dratz, E.A., 1987, The molecular mechanism of visual excitation and its relation to the structure and function of the rod outer segment, *Ann Rev Physiol* 49:765-791.

Lin, J.C., 1978, "Microwave Auditory Effects and Applications," Charles C. Thomas, Springfield, IL.

Lin, J.C. and Lin, M.F., 1980, Studies on microwaves and blood-brain barrier interaction, *Bioelectromagnetics* 1:313-323.

Lin, J.C. and Lin, M.F., 1982, Microwave hyperthermia-induced blood-brain barrier alterations, *Radiat Res* 89:77-87.

Lin-Liu, S., and Adey, W.R., 1982, Low frequency amplitude modulated microwave fields change calcium efflux rate from synaptosomes, *Bioelectromagnetics* 3:309-322.

Lippa, A.S., Klepner, C.A., Yunger, L., Sano, M.C., Smith, W.V., and Beer, B., 1978, Relationship between benzodiazepine receptors and experimental anxiety in rats, *Pharmac Biochem Behav* 9:853-856.

Lobanova, Ye. A., 1974a, Investigation on the susceptibility of animal to microwave irradiation following treatment with pharmacologic agents, *in*: "Biological Effects of Radiofrequency Electromagnetic Fields," Z.V. Gordon, ed., NTIS:JPRS 63321.

Lobanova, Ye. A., 1974b, The dependence of the temperature response to microwave irradiation and the initial functional state of the CNS, *in*: "Biological Effects of Radiofrequency Electromagnetic Fields," Z.V. Gordon, ed., NTIS:JPRS 63321.

Lovely, R.H., and Guy, A.W., 1975, Conditioned taste aversion in the rat induced by a single exposure to microwave, paper presented at the IMPI Microwave Power Symposium, University of Waterloo, Waterloo, Ontario, Canada.

Lovely, R.H., Myers, D.E., and Guy, A.W., 1977, Irradiation of rats by 918-MHz microwaves at 2.5 mW/cm^2: delineating the dose-response relationship, *Radio Sci* 12(6):139-146.

Lu, S.T., Lotz, W.G., and Michaelson, S.M., 1980, Advances in microwave-induced neuroendocrine effects: the concept of stress, *Proc IEEE* 68:73-77.

Lucchi, L., Moresco, R.M., Govoni, S., and Trabucchi, M., 1988, Effect of chronic ethanol treatment on dopamine receptor subtypes in rat striatum, *Brain Res* 449:347-351.

Mansour, A., Khachaturian, H., Lewis, M.E., Akil, H., and Watson, S.J., 1987, Autoradiographic differentiation of mu, delta, and kappa opioid receptors in the rat forebrain, *J Neurosci* 7:2445-2464.

Mackintosh, N.J., 1974, "The Psychology of Animal Learning," Academic Press, New York, NY.

Marr, M.J., de Lorge, J.O., Olsen, R.G., and Stanford, M., 1988, Microwaves as reinforcing events in a cold environment, *in*: "Electromagnetic Fields and Neurobehavioral Functions," M.E. O'Connor and R.H. Lovely, eds., *Prog Clin Biol Res* 257:219-234.

McAfee, R.D., 1961, Neurological effect of 3 cm microwave radiation, *Am J Physiol* 200: 192-199.

McAfee, R.D., 1963, Physiological effects of thermode and microwave stimulation of peripheral nerves, *Am J Physiol* 203: 374-380.

McKee., A., Dorsey, C.H., Eisenbrandt, D.L., and Woden, 1980, Ultrastructural observations of microwave-induced morphologic changes in the central nervous system of hamster, *Bioelectromagnetics* 1:206.

McRee, D.J., and Davis, H.G., 1984, Whole-body and local dosimetry on rats exposed to 2.45-GHz microwave radiation, *Health Phys* 46:315-320.

Medina, J.H., Novas, M.L., and DeRobertis, E., 1983a, Changes in benzodiazepine receptors by acute stress: different effects of chronic diazepam on R015-1788 treatment, *Eur J Pharmacol* 96:181-185.

Medina, J.H., Novas, M.L., Wolfman, C.N.V., Levi DeStein, M., and DeRobertis, E., 1983b, Benzodiazepine receptors in rat cerebral cortex and hippocampus undergo rapid and reversible changes after acute stress, *Neurosci* 9:331-335.

Merritt, J.H., Hartzell, R.H., and Frazer, J.W., 1976, The effect of 1.6 GHz radiation on neurotransmitters in discrete areas of the rat brain, *in*: "Biological Effects of Electromagnetic Waves," vol. 1, C.C. Johnson and M.C. Shore, eds., HEW Publication (FDA) 77-8010, Rockville, MD.

Merritt, J.H., Chamness, A.F., Hartzell, R.H., and Allan, S.J., 1977, Orientation effect on microwave-induced hyperthermia and neurochemical correlates, *J Microwave Power* 12:167-172.

Merritt, J.H., Chamness, A.F., and Allens, S.J., 1978, Studies on blood-brain barrier permeability after microwave radiation, *Radiat Environ Biophys* 15:367-377.

Merritt, J.H., Shelton, W.W., and Chamness, A.F., 1982, Attempts to alter $^{45}Ca^{2+}$ binding to brain tissue with pulse-modulated microwave energy, *Bioelectromagnetics* 3:475-478.

Michaelson, S.M. and Lin, J.C., 1987, "Biological Effects and Health Implications of Radiofrequency Radiation," Plenum Press, New York, NY.

Michaelson, S.M., Thomson, R.A.E., and Howland, J.W., 1961, Physiological aspects of microwave irradiation of mammals, *Am J Physiol* 201:351-356.

Miller, D.B., Christopher, J.P., Hunter, J., and Yeandle, S.S., 1984, The effect of exposure of acetylcholinesterase to 2450 MHz microwave radiation, *Bioelectromagnetics* 5:165-172.

Mitchell, C.L., McRee, D.J., Peterson, N.J., and Tilson, H.A., 1988, Some behavioral effects of short-term exposure of rats to 2.45-GHz microwave radiation, *Bioelectromagnetics* 9:259-268.

Mitchell, D.S., Switzer, W.G., and Bronaugh, E.L., 1977, Hyperactivity and disruption of operant behavior in rats after multiple exposure to microwave radiation, *Radio Sci* 12(6):263-271.

Mizukawa, K., Takayama, H., Sato, H., Ota, J., Haba, K., and Ogawa, N., 1989, Alterations of muscarinic cholinergic receptors in the hippocampal formation of stressed rat: in vitro quantitative autoradiographic analysis, *Brain Res* 478:187-192.

Modak, A.T., Stavinoha, W.B., and Dean, U.P., 1981, Effect of short electromagnetic pulses on brain acetylcholine content and spontaneous motor activity in mice, *Bioelectromagnetics* 2:89-92.

Moe, K.E., Lovely, R.H., Meyers D.E., and Guy, A.W., 1976, Physiological and behavioral effects of chronic low-level microwave radiation in rats, *in*: "Biological Effects of Electromagnetic Waves," vol. 1, C.C. Johnson and M.L. Shore, eds., HEW Publication (FDA) 77-8010, Rockville, MD.

Mohler, H., and Okada, T., 1977, Benzodiazepine receptor: demonstration in the central nervous system, *Science* 198:849-851.

Monahan, J.C., 1988, Microwave-drug interactions in the cholinergic nervous system of the mouse, *in*: "Electromagnetic Fields and Neurobehavioral Function," M.E. O'Connor and D.H. Lovely, eds., *Prog Clin Biol Res* 257:309-326.

Monahan, J.C., and Henton, W., 1977a, Microwave absorption and taste aversion as a function of 915 MHz radiation, *in*: "Symposium on Biological Effects and Measurement of Radio Frequency Microwaves," D.J. Hazzard, ed., HEW Publication (FDA) 77-8026, Rockville, MD.

Monahan, J.C., and Henton, W., 1977b, Free-operant avoidance and escape from microwave radiation, *in*: "Symposium on Biological Effects and Measurement of Radio Frequency Microwaves," D.J. Hazzard, ed., HEW Publication (FDA) 77-8026, Rockville, MD.

Monahan, J.C., and Henton, W., 1979, The effect of psychoactive drugs on operant behavior induced by microwave radiation, *Radio Sci* 14(6):233-238.

Monahan, J.C., and Ho, H., 1976, Microwave-induced avoidance behavior in the mouse, *in*: "Biological Effects of Electromagnetic Waves, Selected Papers of the USNC/URSI Annual Meeting," vol . 1, C.C. Johnson and M.L. Shore , eds., HEW Publication (FDA) 77-8010, Rockville, MD.

Mowrer, W.H., 1939, A stimulus-response analysis of anxiety and its role as a reinforcing agent, *Pychol Rev* 46:553-565.

Muller, P., Britton, R.S., and Seeman, P., 1980, The effect of long-term ethanol on brain receptors for dopamine, acetylcholine, seratonin and noradrenaline, *Eur J Pharmacol* 65:31-37.

Neilly, J.P. and Lin, J.C., 1986, Interaction of ethanol and microwaves on the blood-brain barrier of rats, *Bioelectromagnetics* 7:405-414.

Neubauer, C., Phelan, A.M., Kues, H., and Lange, D.G., 1990, Microwave irradiation of rats at 2.45 GHz activates pinocytotic-like uptake of tracer by capillary endothelial cells of cerebral cortex, *Bioelectromagnetics* 11:261-268.

Nichols, M.L., Hubbell, C.L., Kalsher, M.J., and Reid, L.D., 1991, Morphine increases intake of beer among rats, *Alcohol* 8:237-240.

O'Connor, M.E., 1988, Prenatal microwave exposure and behavior, *in*: "Electromagnetic Fields and Neurobehavioral Function," M.E. O'Connor and R.H. Lovely, eds., *Prog Clin Biol Res* 257:265-288.

Oscar, K.J. and Hawkins, T.D., 1977, Microwave alteration of the blood-brain barrier system of rats, *Brain Res* 126:281-293.

Oscar, K.J., Gruenace, S.P., Folker, M.T., and Rapoport S.L., 1981, Local cerebral blood flow after microwave exposure, *Brain Res* 204:220-225.

Overstreet, D.H., and Yamamura, H., 1979, Receptor alteration and drug tolerance, *Life Sci* 25:1865-1878.

Panksepp, J., Zolovick, A.J., Jalowiec, J.E., Stern, W.C., and Morgane, P.J., 1973, Fenfluramine: effects on aggression, *Biol Psychiat* 6:181-186.

Pappas, B.A., Anisman, H., Ings, R., and Hill, D.A., 1983, Acute exposure to pulsed microwaves affects neither pentylenetetrazol seizures in the rat nor cholordiazepoxide protection against such seizures, *Radiat Res* 96:486-496.

Pickard, W.F., and Barsoum, Y.M., 1981, Radiofrequency bioeffects at the membrane level: separation of thermal and athermal contributions in the Characeae, *J Membrane Biol* 61:39-54.

Plotnikoff, N., Murgo, A., Faith, R., and Wybran, J., eds., 1991, "Stress and Immunity," CRC Press, Boca Raton, FL.

Polc, P., 1988, Electrophysiology of benzodiazepine receptor ligands: multiple mechanisms and sites of action, *Prog Neurobiol* 31:349-424.

Preston, E., and Prefontaine, G., 1980, Cerebrovascular permeability to sucrose in the rat exposed to 2450-MHz microwaves, *J Appl Physiol* 49:218-223.

Preston, E., Vavasour, E.J., and Assenheim, H.M., 1979, Permeability of the blood-brain barrier to mannitol in the rat following 2450 MHz microwave irradiation, *Brain Res* 174:109-117.

Price, D.L., Cork, L.C., Struble, R.G., Whitehouse, P.J., Kitt, C.A., and Walker, L.C., 1985, The functional organization of the basal forebrain cholinergic systems in primates and the role of the system in Alzheimer's disease, *Ann N Y Acad Sci* 444:287-295.

Quock, R.M., Fujimoto, J.M., Ishii, T.K., and Lange, D.G., 1986a, Microwave facilitation of methylatropine antagonism of central cholinomimetic drug effects, *Radiat Res* 105:328-340.

Quock, R.M., Konchich, F.J., Ishii, T.K. and Lange, D.G., 1986b, Microwave facilitation of methylatrophine antagonism of morphine-induced analgesic in mice, *J Bioelectricity* 5:35-46.

Quock, R.M., Konchich, F.J., Ishii, T.K., and Lange, D.G., 1987, Microwave facilitation of domperidone antagonism of apomorphine-induced stereotypic climbing in mice, *Bioelectromagnetics* 8:45-55.

Quock, R.M., Bixby, R.R., Klauenberg, B.J., and Merritt, J.H., 1990, Influence of microwave exposure on chlordiazepoxide effects in the mouse staircase test, *Abst Ann Meeting Bioelectromagnetics Soc* 12:92.

Reid, L.D., Delconte, J.D., Nichols, M.L., Bilsky, E.J., and Hubbell, C.L., 1991, Tests of opioid deficiency hypothesis of alcoholism, *Alcohol* 8:247-257.

Reynolds, G.S., 1968, "Primer of Operant Conditioning," Scott & Foreman, Glenview, IL.

Roberti, B., Heebels, G.H., Hendricx, J.C.M., deGreef, A.H.A.M., and Wolthuis, O.L., 1975, Preliminary investigation of the effect of low-level microwave radiation on spontaneous motor activity in rats, *Ann NY Acad Sci* 247:417-424.

Rudnev, M., Bokina, A., Eksler, N., and Navakatikyan, M., 1978, The use of evoked potential and behavioral measures in the assessment of environmental insult *in*: "Multidisciplinary Perspectives in Event-Related Brain Potential Research," D.A. Otto, ed., EPA-600/9-77-043, U.S. Environmental Protection Agency, Research Triangle Park, NC.

Sagan, P.M., and Medici, R.G., 1979, Behavior of chicks exposed to low-power 450-MHz fields sinusoidally modulated at EEG frequencies, *Radio Sci* 14(6):239-245.

Sanders, A.P., and Joines, W.T., 1984, The effects of hyperthermia and hyperthermia plus microwaves on rat brain energy metabolism, *Bioelectromagnetics* 5:63-70.

Sanders, A.P., Schaefer, D.J., and Joines, W.T., 1980, Microwave effects on energy metabolism of rat brain, *Bioelectromagnetics* 1:171-182.

Sanders, A.P., Joines, W.T., and Allis, J.W., 1984, The differential effect of 200, 591, and 2450 MHz radiation on rat brain energy metabolism, *Bioelectromagnetics* 5:419-433.

Sanders, A.P., Joines, W.T., and Allis, J.W., 1985, Effect of continuous-wave, pulsed, and sinusoidal-amplitude-modulated microwaves on brain energy metabolism, *Bioelectromagnetics* 6:89-97.

Sanza, J.N., and de Lorge, J., 1977, Fixed interval behavior and rats exposed to microwaves at low power densities, *Radio Sci* 12(6):273-277.

Scheich, H., Langner, G., Tidemann, C., Coles, R.B., and Guppy, A., 1986, Electro-reception and electrolocation in platypus, *Nature* 319:401-402.

Scholl, D.M., and Allen, S.J., 1979, Skilled visual-motor performance by monkeys in a 1.2-GHz microwave field, *Radio Sci* 14(6): 247-252.

Schrot, J., Thomas, J.R., and Banvard, R.A., 1980, Modification of the repeated acquisition of response sequences in rats by low-level microwave exposure, *Bioelectromagnetics* 1:89-99.

Schwan, H.P., 1971, Interaction of microwave and radiofrequency radiation with biological systems, *IEEE Microwave Th Tech* MTT-19:146-150.

Schwan, H.P., 1977, Electrical membrane potentials, tissue excitation, and various relevant interpretations, *in*: "Biologic Effects of Electric and Magnetic Fields Associated with Proposed Project Seafarer," National Academy of Sciences, Washington, DC.

Seaman, R.L., and Lebovitz, R.M., 1987, Auditory unit responses to single pulse and twin-pulse microwave stimuli, *Hearing Res* 26:105-116.

Seaman, R.L., and Lebovitz, R.M., 1989, Thresholds of cat cochlea nucleus neurons to microwave pulses, *Bioelectromagnetics* 10:147-160.

Seaman, R.L., and Wachtel, H., 1978, Slow and rapid responses to CW and pulsed microwave radiation by individual Aplysia pacemakers, *J Microwave Power* 13:77-86.

Servantie, B., Batharion, G., Joly, R., Servantie, A.M., Etienne, J., Dreyfus, P., and Escoubet, P., 1974, Pharmacologic effects of a pulsed microwave field, *in*: "Biological Effects and Health Hazards of Microwave Radiation: Proceedings of an International Symposium," P. Czerski, et al., eds., Polish Medical Publishers, Warsaw.

Servantie, B., Servantie, A.M., and Etienne, J., 1975, Synchronization of cortical neurons by a pulsed microwave field as evidenced by spectral analysis of electrocorticograms from the white rat, *Ann N Y Acad Sci* 247:82-86.

Shandala, M.G., Dumanski, U.D., Rudnev, M.I., Ershova, L.K., and Los, I.P., 1979, Study of nonionizing microwave radiation effects upon the central nervous system and behavior reaction, *Environ Health Perspect* 30:115-121.

Shelton, W.W., Jr., and Merritt, J.H., 1981, In vitro study of microwave effects on calcium efflux in rat brain tissue, *Bioelectromagnetics* 2:161-167.

Sheppard, A.R., Bawin, S.M., and Adey, W.R., 1979, Models of long-range order in cerebral macro-molecules: effect of sub-ELF and of modulated VHF and UHF fields, *Radio Sci* 14:141-145.

Siegel, S., 1977, Morphine tolerance acquisition as an associative process, *J Comp Physiol Psychol* 3:1-13.

Siegel, S., Hinson, R.E., Krank, M.D., and McCully, J., 1982, Heroin "overdose" death: contribution of drug-associated environmental cues, *Science* 216:436-437.

Snyder, S.H., 1971, The effect of microwave irradiation on the turnover rate of serotonin and norepinephrine and the effect of microwave metabolizing enzymes, Final Report, Contract No. DADA 17-69-C-9144, U.S. Army Medical Research and Development Command, Washington, DC (NTLT AD-729 161).

Solomon, R.L., and Wynne, L.C., 1954, Traumatic avoidance learning: the principles of anxiety conservation and partial irreversibility, *Psychol Rev* 61:353-385.

Soubrie, P., Thiebot, M.H., Jobert, A., Montastruc, J.L., Hery, F., and Hamon, M., 1980, Decreased convulsant potency of picotoxin and pentetrazol and enhanced [^{3}H] flunitrazepam cortical binding following stressful manipulations in rat, *Brain Res* 189:505-519.

Stavinoha, W.B., Medina, M.A., Frazer, J., Weintraub, S.T., Ross, D.H., Modak, A.T., and Jones, D.J., 1976, The effects of 19 megacycle irradiation on mice and rats, *in*: "Biological Effects of Electromagnetic Waves," vol. 1, C.C. Johnson and M.L. Shore, eds., HEW Publication (FDA) 77-8010, Rockville, MD.

Steriade, M., and Biesold, D. eds., 1990, "Brain Cholinergic Systems," Oxford University Press, Oxford.

Stern, S., 1980, Behavioral effects of microwaves, *Neurobehav Toxicol* 2:49-58.

Stverak, I., Martha, K., and Pafkova, G., 1974, Some effects of various pulsed field on animals with audiogenic epilepsy, *in*: "Biological Effects and Health Hazards of Microwave Radiation: Proceedings of an International Symposium," P. Czerski, et al., eds., Polish Medical Publishers, Warsaw.

Stryer, L., 1987, The molecules of visual excitation, *Scientific American* 257(1):32-40.

Sutton, C.H., and Carroll, F.B., 1979, Effects of microwave-induced hyperthermia on the blood-brain barrier of the rat, *Radio Sci* 14:329-334.

Switzer, W.G., and Mitchell, D.S., 1977, Long-term effects of 2.45 GHz radiation on the ultrastructure of the cerebral cortex and hematologic profiles of rats, *Radio Sci* 12:287-293.

Syvalahti, E.K.G., Hietala, J., Roytta, M., and Gronroos, J., 1988, Decrease in the number of rat brain dopamine and muscarinic receptors after chronic alcohol intake, *Pharmacol Toxicol* 62:210-212.

Tabakoff, B., and Hoffman, P.L., 1979, Development of functional dependence on ethanol in dopaminergic systems, *J Pharmacol Exp Ther* 208:216-222.

Takashima, S., Onaral, B., and Schwan, H.P., 1979, Effects of modulated RF energy on the EEG of mammalian brain, *Rad Environ Biophys* 16:15-27.

Taylor, E.M., and Ashleman, B.T., 1974, Analysis of central nervous system involvement in the microwave auditory effect, *Brain Res* 74:201-208.

Taylor, E.M., and Ashleman, B.T., 1975, Some effects of electromagnetic radiation on the brain and spinal cord of cats, *Ann NY Acad Sci* 247:63-73.

Thomas, J.R., and Maitland, G., 1979, Microwave radiation and dextroamphetamine: evidence of combined effects on behavior of rats, *Radio Sci* 14(6):253-258.

Thomas, J.R., Finch, E.D., Fulk, D.W., and Burch, L.S., 1975, Effects of low level microwave radiation on behavioral baselines, *Ann NY Acad Sci* 247:425-432.

Thomas, J.R., Yeandle, S.S., and Burch, L.S., 1976, Modification of internal discriminative stimulus control of behavior by low levels of pulsed microwave radiation, *in*: "Biological Effects of Electromagnetic Waves," vol. 1, C.C. Johnson and M.L.Shore, eds., HEW Publication (FDA) 77-8010, Rockville, MD.

Thomas, J.R., Burch, L.S., and Yeandle, S.C., 1979, Microwave radiation and chlordiazepoxide: synergistic effects on fixed interval behavior, *Science* 203:1357-1358.

Thomas, J.R., Schrot, J., and Banvard, R.A., 1980, Behavioral effects of chlorpromazine and diazepam combined with low level microwaves, *Neurobiol* 2:131-135.

Tolgskaya, M.S., and Gordon, Z.V., 1973, Pathological effects of radiowaves, (Translated from Russian by B. Haigh), Consultants Bureau, New York, NY.

Wachtel, H., Seaman, R., and Joines, W., 1975, Effects of low-intensity microwaves on isolated neurons, *Ann NY Acad Sci* 247:46-62.

Wangemann, R.T., and Cleary, S.F., 1976, The in vivo effects of 2.45-GHz microwave radiation on rabbit serum components and sleeping times, *Radiat Environ Biophys* 13:89-103.

Ward, T.R., Elder, J.A., Long, M.D., and Svendsgaard, D., 1982, Measurement of blood-brain barrier permeation in rats during exposure to 2450-MHz microwaves, *Bioelectromagnetics* 3:371-383.

Ward, T.R., and Ali, J.S., 1985, Blood-brain barrier permeation in the rat during exposure to low-power 1.7-GHz microwave radiation, *Bioelectromagnetics* 2:131-143.

Ward, T.R., Svensgaard, D.J., Spiegel, R.J., Puckett, E.T., Long, M.D., and Kinn, J.B., 1986, Brain temperature measurements in rats: a comparison of microwave and ambient temperature exposures, *Bioelectromagnetics* 7:243-258.

Weizman, R., Weizman, A., Kook, K.A., Vocci, F., Deutsch, S.I., and Paul, S.M., 1989, Repeated swim stress alters brain benzodiazepine receptors measured in vivo, *J Pharmacol Exp Ther* 249:701-707.

Wild, K.D., and Reid, L.D., 1990, Modulation of ethanol-intake by morphine: evidence for a central site of action, *Life Sci* 47:PL-49-PL-54.

Williams, W.M., Hoss, W., Formaniak, M., and Michaelson, S.M., 1984a, Effect of 2450 MHz microwave energy on the blood-brain barrier to hydrophilic molecules, A. Effect on the permeability to sodium fluorescein, *Brain Res Rev* 7:165-170.

Williams, W.M., del Cerro, M., and Michaelson, S.M., 1984b, Effect of 2450 MHz microwave energy on the blood-brain barrier to hydrophilic molecules, B. Effect on the permeability to HRP, *Brain Res Rev* 7: 171-181.

Williams, W.M., Platner, J., and Michaelson, S.M., 1984c, Effect of 2450 MHz microwave energy on the blood-brain barrier to hydrophilic molecules, C. Effect on the permeability to ^{14}C-sucrose, *Brain Res Rev* 7:183-190.

Williams, W.M., Lu, S.-T., del Cerro, M., and Michaelson, S.M., 1984d, Effect of 2450 MHz microwave energy on the blood-brain barrier to hydrophilic molecules, D. Brain temperature and blood-brain barrier permeability to hydrophilic tracers, *Brain Res Rev* 7:191-212.

Wikler, A., 1973a, Dynamics of drug dependence: Implications of a conditioning theory for research and treatment, *Arch Gen Psychiat* 28:611-616.

Wikler, A., 1973b, Conditioning of successive adaptive responses to the initial effects of drugs, *Conditioned Reflex* 8:193-210.

Wilson, B.A., Zook, J.M., Joines, W.T., and Casseday, J.H., 1980, Alterations in activity at auditory nuclei of the rat induced by exposure to microwave radiation: autoradiographic evidence using [^{14}C]-2-deoxy-D-glucose, *Brain Res* 187:291-306.

Woods, S.C., Makous, W., and Hutton, R.A., 1969, Temporal parameters of conditioned hypoglycemia, *J Comp Physiol Psychol* 69:301-307.

Young, W., 1980, The effect of microwaves (9.7 GHz) on membrane bound acetylcholinesterase in the vagal heart system, *Fed Proc* 39:410.

Zeman, G.H., Chaput, R.L., Glazer, Z.R., and Gershman, L.L., 1973, Gamma-aminobutyric acid metabolism in rats following microwave exposure. *J Microwave Power* 8:213-216.

Appendix 9-B - Memory and Behavior

Presention: The Biological Effects, Health Consequences and Standards for Pulsed Radiofrequency Field. International Commission on Nonionizing Radiation Protection and the World Health Organization, Ettoll Majorare, Centre for Scientific Culture, Italy, 1999.

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The nervous system is very sensitive to environmental disturbance. In the proceedings of an international symposium on the "Biological Effects and Health Hazard of Microwave Radiation" hold in Warsaw, Poland in 1973, it was stated in a summary section that 'the reaction of the central nervous system to microwaves may serve as an early indicator of disturbances in regulatory functions of many systems' [Czerski et al., 1974].

Disturbance to the nervous system leads to behavioral changes. On the other hand, alteration in behavior would imply a change in function of the nervous system. Studies on the effect of radiofrequency radiation (RFR) on behavior have been carried out since the beginning of Bioelectromagnetics research. Some of these studies are briefly reviewed below.

It has been speculated that a pulsed RFR is more potent than its continuous-wave (CW) counterpart in causing biological effects [e.g., Barenski, 1972; Frey et al., 1975; Oscar and Hawkins, 1977]. To evaluate this, it is necessary to compare the effects of pulsed RFR with those of CW radiation. Thus, studies on both CW and pulsed (and frequency-modulated) RFRs are included in this review. Comparing the effects of CW and pulsed RFR can actually be related to the popular debate on the distinction between 'thermal' and 'non-thermal/athermal' effect. If an effect is elicited by a pulsed RFR but not by a CW RFR of the same frequency and intensity under the same exposure conditions, it may imply the existence of 'non-thermal/athermal' effect.

Behavior is generally divided into two main categories: spontaneous and learned. Effects of RFR exposure on both types of behavior have been investigated.

Spontaneous Behavior

Spontaneous behaviors are generally considered to be more resistant to disturbance. The most well studied spontaneous behavior in Bioelectromagnetics research is motor (locomotor) activity. Change in motor activity is generally regarded as an indication of change in the arousal state of an animal.

Hunt et al. [1975] reported decreased motor activity in rats after 30 min of exposure to pulsed 2450-MHz RFR (2.5 msec pulses, 120 pps, SAR 6.3 $W \cdot kg^{-1}$). Mitchell et al. [1988] also

observed a decrease in motor activity in rats after 7 hr of exposure to CW 2450-MHz RFR (10 $mW \cdot cm^{-2}$, average SAR 2.7 $W \cdot kg^{-1}$).

Roberti [1975] reported no significant change in locomotor activity in rats after long-term (185-408 h) exposure to RFR of different frequencies (10.7-GHz CW; 3-GHz CW; 3-GHz with 1.3 ms pulses and 770 pps) and various intensities (SAR 0.15-7.5 $W \cdot kg^{-1}$). Mitchell et al. [1977] reported an increase in motor activity on a small platform of rats exposed to 2450-MHz RFR (CW, average SAR 2.3 $W \cdot kg^{-1}$, 5 hr/day, 5 days/week for 22 weeks). Motor activity of the RFR exposed rats increased during the first week of exposure and stayed higher than controls throughout the period of the experiment. D'Andrea et al. [1979, 1980] reported decreased motor activity on a stabilimetric platform and no significant change in running wheel activity measured overnight in rats exposed to a 2450-MHz RFR (CW, 5 $mW \cdot cm^{-2}$, SAR 1.2 $W \cdot kg^{-1}$, exposed 5 day/week with a total exposure time of 640 hrs, activity was measured every 2-weeks). However, they reported no significant effect in both behaviors in rats similarly exposed to a 915-MHz RFR even at a higher energy absorption rate (CW, 5 $mW \cdot cm^{-2}$, SAR 2.5 $W \cdot kg^{-1}$). Moe et al. [1976] reported a decrease in motor activity of rats exposed to 918 MHz RFR (CW, SAR 3.6-4.2 $W \cdot kg^{-1}$) during the dark period of the light-dark cycle in a chronic exposure experiment (10 hr/night for 3 weeks). Lovely et al. [1977] repeated the experiment using a lower intensity (2.5 $mW \cdot cm^{-2}$, SAR 0.9 $W \cdot kg^{-1}$, 10 hr/night, 13 weeks) and found no significant change in motor activity in the exposed rats. Thus, the threshold of response under their exposure conditions is between1 and 4 $W \cdot kg^{-1}$.

The results from the above studies indicate that it would need a rather high energy absorption rate (>1 $W \cdot kg^{-1}$) to affect motor activity in animals. However, there are two studies reporting effects on motor activity at relatively low SARs. In a long-term exposure study, Johnson et al. [1983] exposed rats to pulsed 2450-MHz RFR (10 ms pulses, 800 pps) from 8 weeks to 25 months of age (22 hr/day). The average whole body SAR varied as the weight of the rats increased and was between 0.4-0.15 $W \cdot kg^{-1}$. Open field activity was measured in 3-min sessions with an electronic open-field apparatus once every 6 weeks during the first 15 months and at 12-week intervals in the final 10 weeks of exposure. They reported a significantly lower open field activity only at the first test session, and a rise in the blood corticosterone level was also observed at that time. The authors speculated that RFR might be 'minimally stressful' to the rats. Rudnev et al. [1978] studied the behavior of rats exposed to CW 2375-MHz RFR at 0.5 $mW \cdot cm^{-2}$ (SAR 0.1 $W \cdot kg^{-1}$), 7 h/day for 1 month. They reported a decrease in balancing time in a treadmill and inclined rod and motor activity in an open-field after 20 days of exposure. The open-field motor activity was found to be increased at 3 months post-exposure. Interestingly, Frey [1977] also reported a decrease in motor coordination on a motor-rod in rats exposed to a 1300-MHz pulsed RFR (0.5 ms pulses, 1000 pps, average power density of 0.65 or 0.2 $mW \cdot cm^{-2}$).

Another type of spontaneous behavior studied was consummatory behavior. In the Rudnev et al. [1978] study, the authors reported a decrease in food intake in their animals after long-term exposure to CW RFR at 0.1 $W \cdot kg^{-1}$. Ray and Behari [1990] also reported a decrease in eating and drinking behavior in rats exposed for 60 days (3 hr/day) to a 7.5-GHz RFR (10-KHz square wave modulation) at an SAR of 0.0317 $W \cdot kg^{-1}$ (average power density 0.6 $mW \cdot cm^{-2}$).

Learned behavior

Several psychological studies have been carried out to investigate whether animals can detect RFR. One of the early studies was that of King et al. [1971] in which RFR was used as

the cue in a conditioned suppression experiment. In conditioned suppression, an animal is first trained to elicit a certain response (e.g., bar-press for food). Once a steady rate of response is attained, a stimulus (e.g., a tone) will be presented to signify the on coming of a negative reinforcement (e.g., electric foot shock). The animal will soon learn the significance of the stimulus and a decrease in responding (conditioned suppression) will occur immediately after the presentation of the stimulus. In the experiment of King et al. [1971], rats were trained to respond at a fixed-ratio schedule for sugar water reward. In a 2-hr session, either a tone or RFR would be presented and occasionally followed by an electric foot shock. Radiofrequency radiation of 2450 MHz, modulated at 12 and 60 Hz and at SARs of 0.6, 1.2, 2.4, 4.8, and 6.4 $W \cdot kg^{-1}$ was used as the conditioned stimulus. With training, consistent conditioned suppression was observed with the radiation at 2.4 $W \cdot kg^{-1}$ and higher. This indicates that rats can detect RFR at 2.4 $W \cdot kg^{-1}$. Monahan and Henton [1977] also demonstrated that mice could be trained to elicit a response in order to escape or avoid RFR (CW, 2450-MHz, 40 $W \cdot kg^{-1}$). In another experiment, Carroll et al. [1980] showed that rats did not learn to go to a 'safe' area in the exposure cage in order to escape exposure to RFR (918-MHz, pulse modulated at 60 Hz, SAR 60 $W \cdot kg^{-1}$) (i.e., entering the 'safe' area resulted in an immediate reduction of the intensity of the radiation), whereas the animals learned readily to escape from electric foot shock by going to the 'safe' area. In a further study from the same laboratory, Levinson et al. [1982] showed that rats could learn to enter a 'safe' area, when the RFR was paired with a light stimulus. Entering the area would turn off both the radiation and light. They also showed that rats could learn to escape by entering the 'safe' area when RFR was presented alone, but learned at a lower rate than when the RFR was paired with a light. All these studies indicate that animals can detect RFR, probably as a thermal stimulus.

One of the most well established effects of pulsed RFR is the 'auditory effect'. Neurophysiological and psychological experiments indicate that animals can probably perceive microwave pulses as a sound stimulus [Chou et al., 1982a; Lin, 1978]. In a series of experiments, Frey and his associates [Frey and Feld, 1975; Frey et al., 1975] demonstrated that rats spent less time in the unshielded compartment of a shuttlebox, when the box was exposed to 1200-MHz pulsed RFR (0.5-ms pulses, 1000 pps, average power density 0.2 $mW \cdot cm^{-2}$, peak power density 2.1 $mW \cdot cm^{-2}$) than during sham exposure. When a CW RFR (1200-MHz, 2.4 $mW \cdot cm^{-2}$) was used, rats showed no significant preference to remain in the shielded or unshielded side of the box. Hjeresen et al. [1979] replicated this finding using pulsed 2880-MHz RFR (2.3 ms pulses, 100 pps, average power density 9.5 $mW \cdot cm^{-2}$) and showed that the preference to remain in the shielded side of a shuttlebox during RFR exposure could be generalized to a 37.5-kHz tone. Masking the 'radiation-induced auditory effect' with a 10-20 kHz noise also prevented shuttlebox-side preference during pulsed RFR exposure. These data indicate that the pulsed RFR-induced 'avoidance' behavior is due to the auditory effect.

The question is why rats avoid pulsed RFR? Is the 'auditory effect' stressful? This question was recently raised by Sienkiewicz [1999]. In an attempt to replicate our radial-arm experiment (Lai et al., 1989), he exposed mice to 900-MHz radiation pulsed at 217 Hz for 45 min a day for 10 days at a whole body SAR of 0.05 $W \cdot kg^{-1}$. He didn't observe any significant effect of RFR exposure on maze learning, but reported that 'some of the exposed animals in our experiment appeared to show a stress-like response during testing in the maze. The animals tested immediately after exposure showed a more erratic performance, and were slower to complete the task compared to the animals tested after a short delay following exposure. This pattern of behavior may be consistent with increased levels of stress.' He also reported that

exposed animals showed increased urination and defecation. He speculated that these behavioral effects were caused by the 'auditory effect' of the pulsed RFR.

Many studies investigated the effects of RFR exposure on schedule-controlled behavior. A schedule is the scheme by which an animal is rewarded (reinforced) for carrying out a certain behavior. For example, an animal can be reinforced for every response it makes, or reinforced intermittently upon responding according to a certain schedule (e.g., once every ten responses). Schedules of different complexity are used in psychological research. The advantage of using reinforcement schedules is that they generate in animals an orderly and reproducible behavioral pattern that can be maintained over a long period of time. This allows a systematic study of the effect of RFR. Generally speaking, more complex behaviors are more susceptible to disruption by environmental factors. However, the underlying neural mechanisms by which different schedules affect behavior are poorly understood.

In a study by D'Andrea et al. [1977], RFRs of different frequencies and intensities were studied on their effects on bar-pressing rate on a variable-interval schedule. It was found that the latency time of stoppage to respond after the radiation was turned on correlated with the rate of rise in body temperature of the animal. Lebovitz [1980] also studied the effects of pulsed 1300-MHz RFR (1 ms pulses, 600 pps) on rats bar-pressing on a fixed-ratio schedule for food reinforcement. A 15-minute 'rewarded' period, when bar pressing was rewarded with food, was followed by a 10-min 'unrewarded' period. Both food reinforced bar presses and unrewarded bar presses during the periods were studied. No significant effect was detected in both types of response at SAR of 1.5 $W{\cdot}kg^{-1}$. However, at 6 $W{\cdot}kg^{-1}$, there was a slight reduction in rewarded bar presses and a large reduction in unrewarded bar presses. The authors concluded that the unrewarded behavior was more susceptible to the effect of RFR than the rewarded behavior. However, Hunt et al. [1975] trained rats to bar press for saccharin water rewards in the presence (5- second duration) of a flashing light and not to respond in the presence of a tone. After 30 min of exposure to 2450-MHz RFR (modulated at 20 Hz, SAR of 6.5 or 11.0 $W{\cdot}kg^{-1}$), rats made more misses at the presence of the light, but there were no significant changes in the incidences of bar-pressing error when the tone was on (unrewarded). Gage [1979] trained rats to alternate responses between 2 levers at 11-30 times for a food reinforcement. Decrement in response rates was observed after 15 hrs of exposure to CW 2450-MHz RFR at 10, 15, and 20 $mW{\cdot}cm^{-2}$ (0.3 $W{\cdot}kg^{-1}$ per $mW{\cdot}cm^{-2}$).

Effects of RFR on more complex operant response sequence and reinforcement schedules were studied in various experiments. de Lorge and Ezell [1980] tested rats on an auditory vigilance (observing-response) behavioral task during exposure to pulsed 5620-MHz (0.5 or 2 ms, 662 pps) and 1280-MHz (3 ms, 370 pps) RFR. In this task, rats had to discriminate two tones in order to press one of two bars appropriately for food reinforcement. The task required continuous sensory-motor activities in which the animal had to coordinate its motor responses according to the stimulus cues (tone) presented. Behavioral decrement was observed at a SAR of 3.75 $W{\cdot}kg^{-1}$ with the 1280-MHz radiation, and at 4.9 $W{\cdot}kg^{-1}$ with the 5620-MHz radiation. The authors concluded that '...the rat's observing behavior is disrupted at a lower power density at 1.28 than at 5.62 GHz because of deeper penetration of energy at the lower frequency, and because of frequency-dependent differences in anatomic distribution of the absorbed microwave energy.' In another experiment, de Lorge [1984] studied rhesus monkeys trained on the auditory vigilance (observing-response) task. After the training, the effects of exposure to RFR of different frequencies (225, 1300, and 5800 MHz) were studied [225-MHz-CW; 1300-MHz- 3 ms pulses, 370 pps; 5800-MHz- 0.5 or 2 ms pulses, 662 pps]. Reduction in performance was

observed at different power density thresholds for the frequencies studied: 8.1 $mW{\cdot}cm^{-2}$ (SAR 3.2 $W{\cdot}kg^{-1}$) for 225 MHz, 57 $mW{\cdot}cm^{-2}$ (SAR 7.4 $W{\cdot}kg^{-1}$) for 1300 MHz, and 140 $mW{\cdot}cm^{-2}$ (SAR 4.3 $W{\cdot}kg^{-1}$) for 5800 MHz. de Lorge concluded that the behavioral disruption under different frequencies of exposure was more correlated with change in body temperature. Disruption occurred when the colonic temperature of the animal had increased by 1°C.

Thomas et al. [1975] trained rats to bar press on two bars: a fixed ratio of 20 on the right bar (20 bar presses produced a food pellet reward) and differential reinforcement of low rate (DRL) on the left bar (bar presses had to be separated by at least 18 sec and no more than 24 sec to produce a reward). There was a time-out period between schedules, i.e., no reinforcement available for responding. Animals were tested 5-10 min after 30 min of exposure to either CW 2450-MHz, pulsed 2860-MHz (1 ms pulses, 500 pps) or pulsed 9600-MHz (1 ms pulses, 500 pps) RFR at various power densities. An increase in DRL response rate was observed with 2450-MHz radiation >7.5 $mW{\cdot}cm^{-2}$ (SAR 2.0 $W{\cdot}kg^{-1}$), 2860-MHz RFR >10 $mW{\cdot}cm^{-2}$ (2.7 $W{\cdot}kg^{-1}$), and 9600-MHz RFR >5 $mW{\cdot}cm^{-2}$ (SAR 1.5 $W{\cdot}kg^{-1}$). A decrease in the rate of response at the fixed ratio schedule was seen in all three frequencies when the power density was greater than 5 $mW{\cdot}cm^{-2}$. In addition, an increase in response rate was observed during time-out periods under irradiation of the three frequencies of RFR at greater than 5 $mW{\cdot}cm^{-2}$. This indicates a disruption of the animals' ability to discriminate the different schedule situations.

Schrot et al. [1980] trained rats to learn a new daily sequence of pressing of three bars for food reinforcement. An increased number of errors and decreased learning rates were observed in the animals after 30 min of exposure to pulsed 2800-MHz RFR (2 ms pulses, 500 pps) at average power densities of 5 and 10 $mW{\cdot}cm^{-2}$ (SAR 0.7 and 1.7 $W{\cdot}kg^{-1}$, respectively). No significant effect on performance was observed at power densities of 0.25, 0.5, and 1 $mW{\cdot}cm^{-2}$.

D'Andrea et al. [1989] studied the behavioral effects of high peak power RFR pulses of 1360-MHz. Rhesus monkeys performing on a complicated reinforcement-schedule involving time-related behavioral tasks (inter-response time, time discrimination, and fixed interval responses) were exposed to high peak power RFR (131.8 $W{\cdot}cm^{-2}$ rms, pulse repetition rate 2-32 Hz). No significant disturbance in performance was observed in the monkeys. Akyel et al. [1991] also studied the effects of exposure to high peak power RFR pulses on behavior. In their experiment, rats pre-trained to bar-press for food reinforcement on either fixed ratio, variable interval, or DRL schedule were exposed for 10 min to 1250-MHz pulses. Each pulse (10 ms width) generated a whole body specific absorption of 2.1 $J{\cdot}kg^{-1}$, which corresponds to a whole body average SAR of 0.21 $mW{\cdot}kg^{-1}$. The pulse rate was adjusted to produce different total doses (0.5-14 $kJ{\cdot}kg^{-1}$). Only at the highest dose (14 $kJ{\cdot}kg^{-1}$), stoppage of responding was observed after exposure, when the colonic temperature was increased by ~2.5°C. Responding resumed when colonic temperature returned to within 1.1°C above the pre-exposure level. When responding resumed, the response rates on the fixed ratio and variable interval schedules were below the pre-exposure base line level. Responses on the DRL schedule were too variable to allow a conclusion to be drawn. The authors concluded that the effect of the high peak power RFR pulses on schedule-controlled behavior was due to hyperthermia.

Several studies investigated the effects of long-term RFR exposure on schedule controlled-behavior. Mitchell et al. [1977] trained rats to respond on a mixed schedule of reinforcement (FR-5 EXT-15 sec), in which 5 responses would give a reward and then a 15 sec lapse time (extinction period) was required before a new response would be rewarded. In addition, the schedule of reinforcement was effective when a lamp was on, while no reinforcement was given when the lamp was off. Rats were then exposed to CW 2450-MHz

RFR (average SAR 2.3 $W{\cdot}kg^{-1}$) for 22 weeks (5 hr/day, 5 days/week) and tested at different times during the exposure period. The RFR-exposed rats showed higher responses during the extinction period, indicating poorer discrimination of the response cues. Navakatikian and Tomashevskaya [1994] described a complex series of experiments in which they observed disruption of a behavior (active avoidance) by RFR. In the study, rats were first trained to perform the behavior and then exposed to either CW 2450-MHz RFR or pulsed 3000-MHz RFR (400-Hz modulation, pulse duration 2 ms, and simulation of radar rotation of 3, 6, and 29 rotations/min) for 0.5-12 hrs or 15-80 days (7-12 hr/day). Behavioral disruption was observed at a power density as low as 0.1 $mW{\cdot}cm^{-2}$ (0.027 $W{\cdot}kg^{-1}$).

Two series of well-designed experiments were run by D'Andrea and his colleagues to investigate the effects of chronic RFR exposure on behavior. In one experiment [D'Andrea et al., 1986 a], rats were exposed for 14 weeks (7 hr/day, 7 days/week) to CW 2450-MHz RFR at 2.5 $mW{\cdot}cm^{-2}$ (SAR 0.7 $W{\cdot}kg^{-1}$). After exposure, the rats were trained to bar press on an interresponse time criterion (IRT). In this schedule, the animals had to respond within 12 to 18 sec after the previous response in order to receive a food reward. Radiofrequency radiation exposed rats emitted more responses during the training period. When the training was completed, the RFR-exposed rats had lower efficiency in bar-pressing to obtain food pellets, i.e., they made more inappropriate responses and received fewer food pellets than the sham-exposed rats during a session. In a signalled two-way active avoidance shuttlebox test, the RFR-exposed rats showed less avoidance response than the sham-exposed rats during training; however, no significant difference in responses in the shuttlebox test was detected at 60 days after exposure between the RFR- and sham-exposed animals. In this experiment, a decrease in the threshold of electric foot shock detection (i.e., increase in sensitivity) was also observed in the irradiated rats during the exposure period, and an increased open-field exploratory behavior was observed in the rats at 30 days post-exposure. It may be interesting to point out that Frey [1977] also reported a decrease in tail pinch-induced aggressive behavior in RFR-exposed rats. Increased latency, decrease in duration, and episodes of fighting after tail pinching were observed between two rats being irradiated with RFR. This could be due to a decreased sensitivity or perception of pain and the RFR-induced activation of endogenous opioids described below.

In a second experiment [D'Andrea et al., 1986 b], rats were exposed to 2450-MHz RFR at 0.5 $mW{\cdot}cm^{-2}$ (SAR 0.14 $W{\cdot}kg^{-1}$) for 90 days (7 hr/day, 7 days/week). Open-field behavior, shuttlebox performance, and schedule-controlled bar-pressing behavior for food pellets were studied at the end of the exposure period. A small deficit in shuttlebox performance and an increased rate of bar-pressing were observed in the RFR exposed rats. Summarizing the data from these two series of experiments [D'Andrea et al., 1986 a,b], D'Andrea and his co-workers concluded that the threshold for the behavioral and physiological effects of chronic RFR exposure in the rats studied in their experiments occurred between the power densities of 0.5 $mW{\cdot}cm^{-2}$ (SAR 0.14 $W{\cdot}kg^{-1}$) and 2.5 $mW{\cdot}cm^{-2}$ (SAR 0.7 $W{\cdot}kg^{-1}$).

In a further experiment, DeWitt et al. [1987] also reported an effect on an operant task in rats after exposure for 7hr/day for 90 days to CW 2450-MHz RFR at a power density of 0.5 $mW{\cdot}cm^{-2}$ (0.14 $W{\cdot}kg^{-1}$).

Little work has been done to investigate the effects of RFR on memory functions. We [Lai et al., 1989] studied the effect of short-term (45 min) RFR exposure (2450-MHz, 2 msec pulses, 500 pps, 1 $mW{\cdot}cm^{-2}$, SAR 0.6 $W{\cdot}kg^{-1}$) on the rats' performance in a radial-arm maze, which measures spatial working (short-term) memory function. The maze consists of a central circular hub with arms radiating out like the spokes of a wheel. In this task, food-deprived

animals are trained to explore the arms of the maze to obtain food reinforcement at the end of each arm. In each session they have to enter each arm once and a reentry is considered as an error. This task requires 'working memory', i.e., the rat has to remember the arms it has already entered during the course of a session. We found that short-term (45 min) exposure to RFR before each session of maze running significantly retarded the rats' abilities to perform in the maze. They made significantly more errors than the sham-exposed rats. In a further experiment [Lai et al., 1994], we found that the RFR-induced working memory deficit in the radial-arm maze was reversed by pretreating the rats before exposure with the cholinergic agonist physostigmine or the opiate antagonist naltrexone, whereas pretreatment with the peripheral opiate antagonist naloxone methiodide showed no reversal of effect. These data indicate that both cholinergic and endogenous opioid neurotransmitter systems inside the central nervous system are involved in the RFR-induced spatial working memory deficit. Spatial working memory requires the functions of the cholinergic innervations in the frontal cortex and hippocampus. The behavior result agrees with our previous neurochemical findings that RFR exposure decreased the activity of the cholinergic systems in the frontal cortex and hippocampus of the rats [Lai et al., 1987]. Endogenous opioids [Lai et al., 1992] and the 'stress hormone' corticotropin-releasing factor [Lai et al., 1990] are also involved. Our hypothesis is that radiofrequency radiation activates endogenous opioids in the brain, which in turn cause a decrease in cholinergic activity leading to short-term memory deficit. Related to this that there is a report by Kunjilwar and Behari [1993] showing that long-term exposure (30-35 days, 3 hrs/day, SAR 0.1-0.14 W/kg) to 147-MHz RFR and its sub-harmonics 73.5 and 36.75 MHz, amplitude modulated at 16 and 76 Hz, decreased acetylcholine esterase activity in the rat brain, whereas short-term exposure (60 min) had no significant effect on the enzyme. There is another report by Krylova et al. [1992] indicating that 'cholinergic system plays an important role in the effects of electromagnetic field on memory processes'. There are also two studies suggesting the involvement of endogenous opioids in the effects of RFR on memory functions [Krylov et al., 1993; Mickley and Cobb, 1998].

In a more recent experiment, we [Wang and Lai, 2000] studied spatial long-term memory using the water maze. In this test, rats are trained to learn the location of a submerged platform in a circular water pool. We found that rats exposed to pulsed 2450-MHz RFR (2 ms pulses, 500 pps, 1.2 $W \cdot kg^{-1}$, 1 hr) were significantly slower in learning and used a different strategy in locating the position of the platform.

Comments

(1) From the data available, it is not apparent that pulsed RFR is more potent than CW RFR in affecting behavior in animals. Even though different frequencies and exposure conditions were used in different studies and hardly any dose-response study was carried out, there is no consistent pattern that the SARs of pulsed RFR reported to cause an effect are lower than those of CW RFR. For example, the Thomas et al [1975] study showed that the thresholds of effect of CW 2450-MHz (2.0 $W \cdot kg^{-1}$) and pulsed 2860-MHz (2.7 $W \cdot kg^{-1}$) radiation on DRL bar-pressing response are quite similar.

(2) Thermal effect is definitely a factor in the effects reported in some of the experiments described above. A related point is that most psychoactive drugs also affect body temperature. Stimulants cause hyperthermia, barbiturates cause hypothermia, and narcotics have a biphasic effect on body temperature (hyperthermia at low doses and hypothermia at high doses). It is not uncommon to

observe a change of 2-3°C within 30 min after a drug is administered. However, in reviewing the literature, there is no general correlation between the effects of psychoactive drugs on body temperature and schedule-controlled behavior. Thus, body temperature may not be a major factor in an animal's responding under schedule-controlled behavior, at least in the case of psychoactive drugs. On the contrary, some of the experiments described above strongly suggest the role of hyperthermia on the RFR effect on the behavior. Perhaps, a sudden and large increase in body temperature as in the case of RFR can have a major effect on responding.

(3) Generally speaking, when effects were observed, RFR disrupted schedule-controlled behavior in animals such as in the cases of discrimination responding [de Lorge and Ezell, 1980; Hunt et al., 1975; Mitchell et al., 1977], learning [Schrot et al., 1980], and avoidance [D'Andrea et al., 1986 a,b]. This is especially true when the task involved complex schedules and response sequence. In no case has an improvement in behavior been reported in animals after RFR exposure. It is puzzling that only disruptions in behavior by RFR exposure are reported. In the studies on EEG, both excitation (desynchronization) and depression (synchronization) have been reported after exposure to RFR [Bawin et al., 1973; Chizhenkova, 1988; Chou et al., 1982b; Dumansky and Shandala, 1974; Goldstein and Sisko, 1974; Takeshima et al., 1979]. Motor activity has also been reported to increase [D'Andrea et al., 1979, 1980; Frey et al., 1975; Hjeresen et al., 1979; Mitchell et al., 1977; Rudnev et al., 1978] and decrease [Hunt et al., 1975; Johnson et al., 1983; Mitchell et al., 1988; Moe et al., 1976; Rudnev et al., 1978] after RFR exposure. If these measurements can be considered as indications of electrophysiological and behavioral arousal and depression, improvement in behavior should occur under certain conditions of RFR exposure. This is especially true with avoidance behavior. Psychomotor stimulants that cause EEG desynchronization and motor activation improve avoidance behavior, whereas tranquilizers that have opposite effects on EEG and motor activity decrease avoidance behavior.

(4) It is difficult to conclude from the effects of RFR on schedule-controlled behavior the underlying neural mechanisms involved. In general, the effects of the effect of RFR on schedule-controlled behavior is similar to those of other agents, e.g., psychoactive drugs. For example, the way that a certain drug affects schedule-controlled behavior depends on the base line level of responding. A general rule is that drugs tend to decrease the rate when the base line responding rate is high and vice versa. This is known as rate-dependency. Exposure to RFR caused a decrease in response rate when a variable interval schedule that produces a steady rate of responding was used [D'Andrea et al., 1976; 1977], and an increase in responding when the DRL-schedule of reinforcement, that produces a low base line of responding, was used [Thomas et al., 1975]. This may reflect a rate-dependency effect. The effect of an agent can also depend on the schedule of reinforcement. For example, amphetamine has different effects on responses maintained on DRL schedule and punishment-suppressed responding schedule, even though both schedules generate a similar low response rate. Stimulus control as a determinant of response outcome was seen in the study of Lebovitz [1980] when unrewarded responses were disrupted more by RFR than rewarded responses, and the study of Hunt et al. [1975] that showed the reverse relationship. In the former experiment a fixed interval schedule was used, whereas in the latter a discrimination paradigm was studied.

(5) It is also interesting to point out that in most of the behavioral experiments, effects were observed after the termination of RFR exposure. In some experiments (e.g., Rudnev et al., 1978; D'Andrea et al., 1986 a,b), tests were made days after exposure. This suggests a persistent change in the nervous system after exposure to RFR.

(6) In many instances, effects on learned behavior were observed at a SAR less than 4 $W{\cdot}kg^{-1}$. (D'Andrea et al [1986a,b] 0.14 to 0.7 $W{\cdot}kg^{-1}$; DeWitt et al. [1987] 0.14 $W{\cdot}kg^{-1}$; Gage [1979] 3 $W{\cdot}kg^{-1}$; King et al.[1971] 2.4 $W{\cdot}kg^{-1}$; Lai et al. [1989] 0.6 $W{\cdot}kg^{-1}$; Mitchell et al. [1977] 2.3 $W{\cdot}kg^{-1}$; Navakatikian and Tomashevskaya [1994] 0.027 $W{\cdot}kg^{-1}$; Schrot et al. [1980] 0.7 $W{\cdot}kg^{-1}$; Thomas et al. [1975] 1.5 to 2.7 $W{\cdot}kg^{-1}$; Wang and Lai [2000] 1.2 $W{\cdot}kg^{-1}$).

(7) Does disturbance in behavior have any relevance to health? The consequence of a behavioral deficit is situation dependent and may not be direct. It probably does not matter if a person is playing chess and RFR in his environment causes him to make a couple of bad moves. However, the consequence would be much more serious if a person is flying an airplane and his response sequences are disrupted by RFR radiation.

References

Akyel, Y., Hunt, E.L., Gambrill, C., and Varga, C. Jr., 1991, Immediate postexposure effects of high-peak-power microwave pulses on operant behavior of Wistar rats, Bioelectromagnetics 12:183-195.

Barenski, S., 1972, Histological and histochemical effects of microwave radiation on the central nervous system of rabbits and guinea pigs, Am J Physiol Med 51:182-190.

Bawin, S.M., Gavalas-Medici, R.J., and Adey, W.R., 1973, Effects of modulated very high frequency fields on specific brain rhythms in cats, Brain Res 58:365-384.

Carroll, D.R., Levinson, D.M., Justesen, D.R., and Clarke, R.L., 1980, Failure of rats to escape from a potenially lethal microwave field, Bioelectromagnetics 1:101-115.

Chizhenkova, R.A., 1988, Slow potentials and spike unit activity of the cerebral cortex of rabbits exposed to microwaves, Bioelectromagnetics 9:337-345.

Chou, C.K., Guy, A.W., and Galambos, R., 1982a, Auditory perception of radiofrequency electromagnetic fields, J Acoust Soc Am 71:1321-1334.

Chou, C.K., Guy, A.W., McDougall, J.B., and Han, L.F., 1982b, Effects of continuous and pulsed chronic microwave exposure on rabbits, Radio Sci 17:185-193.

Czerski, P., Ostrowski, K., Shore, M.L., Silverman, C.H., Sues, M.J., and Waldeskog, B., eds., 1974, "Biological Effects and Health Hazard of Microwave Radiation: Proceedings of an International Symposium," Polish Medical Publisher, Warsaw.

D'Andrea, J.A., Gandhi, O.P., and Kesner, R.P., 1976, Behavioral effects of resonant electromagnetic power absorption in rats. In: "Biological Effects of Electromagnetic Waves," vol 1, C.C. Johnson and M.L. Shore, eds., HEW Publication (FDA) 77-8010, Rockville, MD.

D'Andrea, J.A., Gandhi, O.P., and Lords J.L., 1977, Behavioral and thermal effects of microwave radiation at resonant and nonresonant wavelengths, Radio Sci 12:251-256.

D'Andrea, J.A., Gandhi, O.P., Lords, J.L., Durney, C.H., Johnson, C.C., and Astle, L., 1979, Physiological and behavioral effects of chronic exposure to 2450-MHz microwaves, J Microwave Power 14:351-362.

D'Andrea, J.A., Gandhi, O.P., Lords. J.L., Durney, C.H., Astle, L., Stensaas, L.J., and Schoenberg, A.A., 1980, Physiological and behavioral effects of prolonged exposure to 915 MHz microwaves, J Microwave Power 15(2):123-135.

D'Andrea, J.A., DeWitt, J.R., Emmerson, R.Y., Bailey, C., Stensaas, S., and Gandhi, O. P., 1986a, Intermittent exposure of rat to 2450-MHz microwaves at 2.5 mW/cm^2: behavioral and physiological effects, Bioelectromagnetics 7:315-328.

D'Andrea, J.A., DeWitt, J.R., Gandhi, O. P., Stensaas, S., Lords, J.L., and Nielson, H.C., 1986b, Behavioral and physiological effects of chronic 2450-MHz microwave irradiation of the rat at 0.5 mW/cm^2, Bioelectromagnetics 7:45-56.

D'Andrea, J.A., Cobb, B.L., and de Lorge, J., 1989, Lack of behavioral effects in the rhesus monkey to high peak power microwave pulses at 1.3 GHz, Bioelectromagnetics 10:65-76.

de Lorge, J.O. , 1984, Operant behavior and colonic temperature of Macaca mulatta exposed to radiofrequency fields at and above resonant frequencies. Bioelectromagnetics 5:233-246.

de Lorge, J., and Ezell, C.S., 1980, Observing-responses of rats exposed to 1.28- and 5.62-GHz microwaves, Bioelectromagnetics 1:183-198.

DeWitt, J.R., D'Andrea, J.A., Emmerson, R.Y., and Gandhi, O.P., 1987, Behavioral effects of chronic exposure to 0.5 mW/cm^2 of 2450-MHz microwaves. Bioelectromagnetics 8:149-157.

Dumansky, J.D., and Shandala, M.G., 1974, The biologic action and hygienic significance of electromagnetic fields of super high and ultra high frequencies in densely populated areas. In: "Biologic Effects and Health Hazard of Microwave Radiation: Proceedings of an International Symposium," P. Czerski, et al., eds., Polish Medical Publishers, Warsaw.

Frey, A.H., 1977, Behavioral effects of electromagnetic energy. In: "Symposium on Biological Effects and Measurement of Radio Frequency Microwaves," D.J. Hazzard, ed., HEW Publication (FDA), 77-8026, Rockville, MD.

Frey, A.H., and Feld, S.R., 1975, Avoidance by rats of illumination with low power nonionizing electromagnetic energy, J Comp Physiol Psychol 89:183-188.

Frey, A.H., Feld, S.R., and Frey, B., 1975, Neural function and behavior: defining the relationship. Ann N Y Acad Sci 247:433-439.

Gage, M.I., 1979, Behavior in rats after exposure to various power densities of 2450 MHz microwaves, Neurobehav Toxicol 1:137-143.

Goldstein, L., and Sisko, Z., 1974, A quantitative electroencephalographic study of the acute effect of X-band microwaves in rabbits. In: "Biological Effects and Health Hazards of Microwave Radiation: Proceedings of an International Symposium," P. Czerski, et al., eds., Polish Medical Publishers, Warsaw.

Hjeresen, D.L., Doctor, S.R., and Sheldon, R.L., 1979, Shuttlebox-side preference as mediated by pulsed microwaves and conventional auditory cue. In: "Electromagnetic Fields in Biological System," S.S.Stuchly, ed., Ottawa,Canada.

Hunt, E.L., King, N.W., and Phillips, R.D., 1975, Behavioral effects of pulsed microwave radiation, Ann NY Acad Sci 247:440-453.

Johnson, R.B., Spackman, D., Crowley, J., Thompson, D., Chou, C.K., Kunz, L.L., and Guy, A.W., 1983, Effects of long-term low-level radiofrequency radiation exposure on rats, vol. 4, Open field behavior and corticosterone, USAF SAM-TR83-42, Report of USAF School of Aerospace Medicine, Brooks AFB, San Antonio, TX.

King, N.W., Justesen, D.R., and Clarke, R.L., 1971, Behavioral sensitivity to microwave irradiation, Science 172:398-401.

Krylova, I.N., Dukhanin, A.S., Il'in, A.B., Kuznetsova, E.Iu., Balaeva, N.V., Shimanovskii, N.L., Pal'tsev, Iu.P., and Iasnetsov, V.V., 1992, The effect of ultrahigh frequency electromagnetic radiation on learning and memory processes (article in Russian), Biull Eksp Biol Med 114:483-484.

Krylov, I.N., Iasnetsov, V.V., Dukhanin, A.S., and Pal'tsev, Iu.P., 1993, Pharmacologic correction of learning and memory disorders induced by exposure to high-frequency electromagnetic radiation (article in Russian), Biull Eksp Biol Med 115:260-262.

Kunjilwar, K.K., and Behari, J., 1993, Effect of amplitude-modulated radio frequency radiation on cholinergic system of developing rats, Brain Res 601:321-324.

Lai, H., Horita, A., Chou, C.K., and Guy, A.W., 1987, Low-level microwave irradiation affects central cholinergic activity in the rat, J Neurochem 48:40-45.

Lai, H., Carino, M.A., and Guy, A.W., 1989, Low-level microwave irradiation and central cholinergic systems, Pharmac Biochem Behav 33:131-138.

Lai, H., Carino, M.A., Horita, A. and Guy, A.W., 1990, Corticotropin-releasing factor antagonist blocks microwave-induced changes in central cholinergic activity in the rat, Brain Res Bull 25:609-612.

Lai, H., Carino, M.A., Horita, A. and Guy, A.W., 1992, Opioid receptor subtypes that mediate a microwave-induced decrease in central cholinergic activity in the rat. Bioelectromagnetics 13:237-246.

Lai, H., Horita, A., and Guy, A.W., 1994, Microwave irradiation affects radial-arm maze performance in the rat, Bioelectromagnetics 15:95-104.

Lebovitz, R.M., 1980, Behavioral changes during long-term microwave irradiation. In: "Proceeding of the International Symposium on the Biological Effects of Electromagnetic waves," UNSI, CNFRS, Jouy-en-Josas, France.

Levinson, D.M., Grove, A.M., Clarke, L.R., and Justesen, D.R., 1982, Photic cueing of escape by rats from an intense microwave field, Bioelectromagnetics 3:105-116.

Lin, J.C., 1978, "Microwave Auditory Effects and Applications", Charles C, Thomas, Springfield, IL.

Lovely, R.H., Myers, D.E., and Guy, A.W., 1977, Irradiation of rats by 918-MHz microwaves at 2.5 mW/cm2: delineating the dose-response relationship, Radio Sci 12(6):139-146.

Mickley, G.A. and Cobb, B.L., 1998, Thermal tolerance reduces hyperthermia-induced disruption of working memory: a role for endogenous opiates? Physiol Beh 63:855-865.

Mitchell, C.L., McRee, D.J., Peterson, N.J., and Tilson, H.A., 1988, Some behavioral effects of short-term exposure of rats to 2.45-GHz microwave radiation, Bioelectromagnetics 9:259-268.

Mitchell, D.S., Switzer, W.G., and Bronaugh, E.L., 1977, Hyperactivity and disruption of operant behavior in rats after multiple exposure to microwave radiation, Radio Sci 12(6):263-271.

Moe, K.E., Lovely, R.H., Meyers D.E., and Guy, A.W., 1976, Physiological and behavioral effects of chronic low-level microwave radiation in rats. In: "Biological Effects of Electromagnetic Waves," vol. 1, C.C. Johnson and M.L. Shore, eds., HEW Publication (FDA) 77-8010, Rockville, MD.

Monahan, J.C., and Henton, W., 1977, Free operant avoidance and escape from microwave radiation. In: "Symposium on Biological Effects and Measurement of Radio Frequency Microwaves", D.J. Hazzard, ed, HEW Publication (FDA) 77-8026, Rockville, MD.

Navakatikian, M.A., and Tomashevskaya, L.A., 1994, Phasic behavioral and endocrine effects of microwaves of nonthermal intensity. In: "Biological Effects of Electric and Magnetic Fields, vol. 1", D.O. Carpenter, ed., Academic Press, San Diego, CA.

Oscar, K.J., and Hawkins, T.D., 1977, Microwave alteration of the blood-brain barrier system of rats, Brain Res 126:281-293.

Ray, S., and Behari, J., 1990, Physiological changes in rats after exposure to low levels of microwaves. Rad Res 123:199-202.

Roberti, B., Heebels, G.H., Hendricx, J.C.M., deGreef, A.H.A.M., and Wolthuis, O.L., 1975, Preliminary investigation of the effect of low-level microwave radiation on spontaneous motor activity in rats, Ann NY Acad Sci 247:417-424.

Rudnev, M., Bokina, A., Eksler, N., and Navakatikyan, M., 1978, The use of evoked potential and behavioral measures in the assessment of environmental insult. In: "Multidisciplinary Perspectives in Event-Related Brain Potential Research," D.A. Otto, ed., EPA-600/9-77-043, U.S. Environmental Protection Agency, Research Triangle Park, NC.

Schrot, J., Thomas, J.R., and Banvard, R.A., 1980, Modification of the repeated acquisition of response sequences in rats by low-level microwave exposure, Bioelectromagnetics 1:89-99.

Schwan, H.P., 1971, Interaction of microwave and radiofrequency radiation with biological systems, IEEE Microwave Th Tech MTT-19:146-150.

Sienkiewicz, Z., 1999, Behavioural effects of radiofrequency fields. In "Mobile Telephones and Health: an Update on the Latest Research", Gothenburg, Sweden.

Takashima, S., Onaral, B., and Schwan, H.P., 1979, Effects of modulated RF energy on the EEG of mammalian brain, Rad Environ Biophys 16:15-27.

Thomas, J.R., Finch, E.D., Fulk, D.W., and Burch, L.S., 1975, Effects of low level microwave radiation on behavioral baselines, Ann NY Acad Sci 247:425-432.

Wang, B.M. and Lai, H., 2000, Acute exposure to pulsed 2450-MHz microwaves affects water-maze performance of rats, Bioelectromagnetics 21:52-56.

SECTION 10 – Part 1

EVIDENCE FOR BRAIN TUMORS AND ACOUSTIC NEUROMAS

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I. Introduction

During the recent decade potential health risks from microwave exposure during use of wireless phones has been discussed both in scientific settings but also by the layman. Especially the use of mobile phones has been of concern, to less extent use of cordless desktop phones (digital enhanced cordless telephone; DECT). The Nordic countries were among the first in the world to widely adopt use of such devices, probably due to the mobile phone companies like Ericsson in Sweden and Nokia in Finland.

These countries may be taken as models for the introduction of this new technology on the market. Thus, the analogue mobile phone system (Nordic Mobile Telephony, NMT) using 450 MHz started to operate in Sweden in 1981. First, it was used in cars with external antenna but from 1984 mobile (portable!) phones existed. This system is still used in Sweden but only to a minor extent. The 900 MHz NMT system operated in Sweden between 1986-2000. The GSM phone (Global System for Mobile communication) started in 1991 and is the most used phone type today, although the 3G phone (third generation mobile phone, UMTS) is increasingly used now.

The risk of brain tumors has been of special concern since the brain is the organ mainly exposed during such phone calls. Most studies on this topic have been of the case-control design and no results exist from prospective cohort studies. However, the results have been hampered by too short tumor-induction period in most studies or with limited number of long-term users, i.e. $\geq$ 10 years latency time. As to carcinogenesis short latency period is of limited value to predict long-term health risks. Usually a latency period of at least 10 years is needed for more firm conclusions. It should noted that for several carcinogens longer latency periods are often

required, such as smoking and lung cancer, asbestos and lung cancer, dioxins and certain cancer types etc.

By now a number of studies exist that give results for brain tumour risk and use of mobile phones for subjects with latency period $\geq$ 10 years. Most of these results are based on low numbers but nevertheless may together give a pattern of increased risk. In this review we discuss all studies on this topic that have been published so far. Moreover, we present a meta-analysis of results from studies with at least 10 years latency period. Only the Hardell group in Sweden has published results also for use of cordless phones. Recently the same group published an overview of long-term use of cellular phones and the risk for brain tumors, especially with use for 10 years or more (Hardell et al 2007). In the following a brief summary is given of these results with the addition of two more study published after that review (Klaeboe et al 2007, Schlehofer et al 2007). For further details see Hardell et al (2007).

II. Materials and Methods

The Pub Med database (**www.ncbi.nlm.nih.gov**) was used for an up-dated search of published studies in this area using mobile/cellular/cordless telephone and brain tumour/neoplasm/acoustic neuroma/meningioma/glioma as searching terms. Personal knowledge of published studies was also used in order to get as comprehensive review as possible. Regarding several publication of the same study the most recent one with relevant data was used. We identified 20 studies to be included. Two were cohort studies (one study analysed twice) and 18 were case-control studies. No mortality studies were included. Three studies came from USA, four from Denmark, one from Finland, five from Sweden, two from Germany, one from the UK, one from Japan, one from Norway and two from study groups partly overlapping previously mentioned studies.

III. Results

A. The first Swedish studies

The first study by Hardell et al (1999, 2001) included cases and controls collected during 1994-96 in Sweden. Only living cases were included. Two controls were selected to each case from the Population Registry. The questionnaire was answered by 217 (93 %) cases and 439 (94 %) controls. Overall no association between mobile phone use and brain tumours was found, but when analysing ipsilateral phone use a somewhat increased risk was seen especially for tumours in the temporal, occipital or temporoparietal lobe yielding odds ratio (OR) = 2.4, 95 % confidence interval (CI) = 0.97-6.1 (Hardell et al 2001).

Hardell et al (2006a) made a pooled analysis for benign brain tumours from their two case-control studies. Cases were reported from Cancer Registries and controls were population based. The questionnaire was answered by 1,254 (88 %) cases and 2,162 (89 %) controls. Also use of cordless desktop phones was assessed. Use of cellular phones gave for acoustic neuroma OR = 1.7, 95 % CI 1.2-2.3 increasing to OR = 2.9, 95 % CI = 1.6-5.5 with > 10 year latency period. The corresponding results for cordless phones were OR = 1.5, 95 % CI = 1.04-2.0, and OR = 1.0, 95 % CI 0.3-2.9, respectively. Regarding meningioma cellular phones gave OR = 1.1, 95 % CI = 0.9-1.3, and cordless OR = 1.1, 95 % CI = 0.9-1.4. Using > 10 year latency period ORs increased, for cellular telephones OR = 1.5, 95 % CI = 0.98-2.4, and for cordless phones OR = 1.6, 95 % CI = 0.9-2.8.

The pooled analyses of the two case control studies of malignant brain tumours by Hardell et al (2006b) included 905 (90%) cases and the same control group as for benign tumours was used,

2,162 (89 %) subjects. Overall for low-grade astrocytoma cellular phones gave OR= 1.4, 95 % CI = 0.9-2.3 and cordless phones OR = 1.4, 95 % CI = 0.9-3.4. The corresponding results for high-grade astrocytoma were OR = 1.4, 95 % CI = 1.1-1.8, and OR = 1.5, 95 % CI = 1.1-1.9, respectively. Using > 10 year latency period gave for low-grade astrocytoma and use of cellular phones OR = 1.5, 95 % CI = 0.6-3.8 (ipsilateral OR = 1.2, 95 % CI = 0.5-5.8), and for cordless phones OR = 1.6, 95 % CI = 0.5-4.6 (ipsilateral OR = 3.2, 95 % CI = 0.6-16). For high-grade astrocytoma in the same latency period cellular phones gave OR = 3.1, 95 % CI = 2.0-4.6 (ipsilateral OR = 5.4, 95 % CI = 3.0-9.6), and cordless phones OR = 2.2, 95 % CI = 1.3-3.9 (ipsilateral OR = 4.7, 95 % CI = 1.8-13).

B. Studies from USA

Muscat et al (2000) studied patients with malignant brain tumours from five different hospitals in USA. Controls were hospital patients. Data from 469 (82 %) cases and 422 (90 %) controls were available. Overall no association was found, OR for handheld cellular phones was 0.9, 95 % CI = 0.6-1.2, but the mean duration of use was short, only 2.8 years for cases and 2.7 years for controls. For neuroepithelioma OR = 2.1, 95 % CI = 0.9-4.7, was reported. The study is inconclusive since no data were available on long-term users (≥ 10 years latency period). Some support of an association was obtained since of 41 evaluable tumours, 26 occurred at the side of the head mostly used during calls and 15 on the contralateral side.

Also the study by Inskip et al (2001) from USA had few long-term users of mobile phones, only 11 cases with glioma, 6 with meningioma and 5 with acoustic neuroma with ≥ 5 years regular use. No subjects had ≥ 10 years use. The study comprised 489 (92 %) hospital cases with malignant brain tumours, 197 with meningioma and 96 with acoustic neuroma, and 799 (86 %) hospital-based controls. Overall no significant associations were found. Regarding different

types of glioma OR = 1.8, 95 % CI = 0.7-5.1 was found for anaplastic astrocytoma. Duration of use ≥ 5 years gave for acoustic neuroma OR increased to 1.9, 95 % CI = 0.6-5.9.

In another study by Muscat et al (2002) presented results from a hospital based case-control study on acoustic neuroma on 90 (100 %) patients and 86 (100 %) controls. Cell phone use 1-2 years gave OR = 0.5, 95 % CI = 0.2-1.3 (n=7 cases), increasing to OR = 1.7, 95 % CI = 0.5-5.1 (n=11 cases), in the group with 3-6 years use. Average use among cases was 4.1 years and among controls 2.2 years.

C. Danish cohort study

A population based cohort study in Denmark of mobile phone users during 1982 to 1995 included over 700,000 users (Johansen et al 2001). About 200,000 individuals were excluded since they had company paid mobile phones. Of digital (GSM) subscribers only nine cases had used the phone for ≥ 3 years duration yielding standardised incidence ratio (SIR) of 1.2, 95 % CI = 0.6-2.3. No subjects with 10-year use were reported.

This cohort study was updated with follow-up through 2002 for cancer incidence (Schüz et al 2006). There was no truly unexposed group for comparison since a large part of the population uses wireless phones. Moreover the excluded company subscribers (> 200 000 or 32 %) were apparently included in the reference population. There was also a very skewed sex distribution with 85 % men and only 15 % women in the cohort. SIR was significantly decreased to 0.95, 95 % CI = 0.9-0.97 for all cancers indicating a "healthy worker" effect in the study. In the group with ≥ 10 years since first subscription significantly decreased SIR of 0.7, 95 % CI = 0.4-0.95 was found for brain and nervous system tumours indicating methodological problems in the study. No latency data were given or laterality of phone use in relation to tumour localisation in

the brain. This study was uninformative regarding long-term health effects from mobile phone use.

D. Finnish study

Auvinen et al (2002) did a register based case-control study on brain and salivary gland tumors in Finland. All cases aged 20-69 years diagnosed in 1996 were included; 398 brain tumour cases and 34 salivary gland tumour cases. The duration of use was short, for analogue users 2-3 years and for digital less than one year. No association was found for salivary gland tumours. For glioma OR = 2.1, 95 % CI = 1.3-3.4 was calculated for use of analogue phones, but no association was found for digital mobile phones. When duration of use of analogue phones was used as a continuous variable an increased risk was found for glioma with OR = 1.2, 95 % CI = 1.1-1.5 per year of use.

E. The Interphone studies

1. Acoustic neuroma

The Swedish part of the Interphone study on acoustic neuroma included exposure data from 148 (93 %) cases and 604 (72 %) population based controls (Lönn et al 2004). Use of digital phones with time $\geq$ 5 years since first use gave OR = 1.2, 95 % CI = 0.7-2.1. No subjects were reported with use of a digital phone $\geq$ 10 years. An association was found for use of analogue phones yielding for $\geq$ 10 years latency period OR = 1.8, 95 % CI = 0.8-4.3 increasing to OR = 3.9, 95 % CI = 1.6-9.5 for ipsilateral use.

In Denmark the Interphone study included 106 (82 %) interviewed cases with acoustic neuroma and 212 (64 %) population-based controls (Christensen et al 2004). Significantly larger tumours were found among cellular phone users, 1.66 cm^3 compared with 1.39 cm^3 among non-users, p =

0.03. However OR was not significantly increased but only two cases had use a mobile phone regularly ≥ 10 years.

Schoemaker et al (2005) presented results for acoustic neuroma as part of the Interphone study performed in 6 different regions in the Nordic countries and UK, as previously partly reported (Lönn et al 2004; Christensen et al 2004). The results were based on 678 (82 %) cases and 3,553 (42 %) controls. Lifetime use of mobile phone for ≥ 10 years gave for ipsilateral acoustic neuroma OR = 1.8, 95 % CI = 1.1-3.1, and for contralateral OR = 0.9, 95 % CI = 0.5-1.8.

The study from Japan by Takebayashi et al (2006) included 101 (84 %) acoustic neuroma cases aged 30-69 years and diagnosed during 2000-2004. Using random digit dialling 339 (52 %) controls were interview. No association was found, OR = 0.7, 95% CI = 0.4 – 1.2. No exposure related increase in the risk of acoustic neuroma was observed when the cumulative length of use (<4 years, 4-8 years, >8 years) or cumulative call time (<300 hours, 300-900 hours, >900 hours) was used as an exposure index. The OR was 1.1, 95% CI = 0.6 - 2.1, when the reference date was set to five years before the diagnosis. Further, laterality of mobile phone use was not associated with tumours. No cases with ≥10 years latency period were reported.

Use of mobile phones and risk of acoustic neuroma were published from Norway as part of the Interphone study (Klaeboe et al 2007). It included 45 (68 %) acoustic neuroma cases and 358 (69 %) controls. A decreased risk was found with OR = 0.5, 95 % CI = 0.2-1.0. Using different criteria such as duration of regular use, time since first regular use, cumulative use etc 22 additional ORs and CIs were calculated. Time since first regular use for < 6 years gave OR =

1.0, 95 % CI = 0.2-5.7. All 21 other ORs were < 1.0 indicating systematic bias in the study. No case had a latency period of 10 years.

Schlehofer et al (2007) reported results from the German part of the Interphone study on sporadic acoustic neuroma. The study was performed during October 2000 and October 2003. Four study areas were included and cases were aged 30-59 years, but from October 1, 2001 extended to include the age group 60-69 years. They were recruited from hospitals and included 97 (89 %) cases, however, three with trigeminus neuroma. Controls were randomly selected from population registries and in total 202 (55 %) agreed to participate. No association was found for regular mobile phone use, OR = 0.7, 95 % CI = 0.4-1.2. Most ORs were < 1.0 and a decreasing trend of the risk was found for time since first regular use, lifetime number of use and duration of calls. No case had a latency period > 10 years. However, increased OR was found for highly exposed in "specified occupational exposure" yielding OR = 1.5, 95 % CI =0.5-4.2.

E. The Interphone studies

2. Glioma, meningioma

Lönn et al (2005) also studied glioma and meningioma. Data were obtained for 371 (74 %) glioma and 273 (85 %) meningioma cases. The control group consisted of 674 (71 %) subjects. No association was found although time since first regular phone use for $\geq$ 10 years gave for ipsilateral glioma OR = 1.6, 95 % CI = 0.8-3.4 and for contralateral glioma OR = 0.7, 95 % CI = 0.3-1.5.

For ipsilateral meningioma OR = 1.3, 95 % CI = 0.5-3.9 was calculated and for contralateral OR = 0.5, 95 % CI = 0.1-1.7 using 10 $\geq$ years latency period.

The Danish part of the Interphone study on brain tumours (Christensen et al, 2005) included 252 (71 %) persons with glioma, 175 (74 %) with meningioma and 822 (64 %) controls. For meningioma OR = 0.8, 95 % CI = 0.5-1.3 was calculated and for low-grade glioma OR = 1.1, 95 % CI = 0.6-2.0, and for high-grade glioma OR = 0.6, 95 % CI = 0.4-0.9 were found. Use for $\geq$ 10 years yielded for meningioma OR = 1.0, 95 % CI = 0.3-3.2, low-grade glioma OR = 1.6, 95 % CI = 0.4-6.1 and for high-grade glioma OR = 0.5, 95 % CI = 0.2-1.3. Regarding high-grade glioma 17 ORs were presented and all showed OR < 1.0.

Results from England were based on 966 (51 %) glioma cases and 1,716 (45 %) controls (Hepworth et al 2006). Cases were ascertained from multiple sources including hospital departments and cancer registries. The controls were randomly selected from general practioners' lists. Regular phone use gave OR = 0.9, 95 % CI = 0.8-1.1, increasing to OR = 1.2, 95 % CI = 1.02-1.5 for ipsilateral use but OR = 0.8, 95 % CI = 0.6-0.9 for contralateral use. Ipsilateral use for $\geq$ 10 years produced OR = 1.6, 95 % CI = 0.9-2.8, and contralateral OR = 0.8, 95 % CI = 0.4-1.4.

Schüz et al (2006) carried out a population-based case-control study in three regions of Germany, with incident cases of glioma and meningioma aged 30-69 years during 2000-2003. Controls were randomly drawn from population registries. In total, 366 (80 %) glioma cases, 381 (88 %) meningioma cases, and 1,494 (61 %) controls were interviewed. For glioma OR = 1.0, 95% CI = 0.7 - 1.3 and for meningioma OR = 0.8, 95% CI = 0.6 - 1.1 were obtained. However, among persons who had used cellular phones for $\geq$ 10 years increased risk was found for glioma; OR = 2.2, 95% CI = 0.9 - 5.1 but not for meningioma; OR = 1.1, 95% CI = 0.4 – 3.4. Among women they found OR = 2.0, 95 % CI = 1.1-3.5 for high-grade glioma for "regular" cell-phone use.

Summary results for mobile phone use and risk of glioma in Denmark, and parts of Finland, Norway, Sweden and United Kingdom have been published (Lahkola et al 2007). Of the included Interphone studies results had already been published from Sweden (Lönn et al 2005), Denmark (Christensen et al 2005) and UK (Hepworth et al 2006). The results were based on 2,530 eligible cases but only 1,521 (60%) participated. Regular mobile phone use gave OR = 0.8, 95 % CI = 0.7-0.9, but cumulative hours of use yielded OR = 1.006, 95 % CI = 1.002-1.010 per 100 hours. Ipsilateral mobile phone use for $\geq$ 10 years gave OR = 1.4, 95 % CI = 1.01-1.9, *p* trend = 0.04 and contralateral use OR = 1.0, 95 % CI = 0.7-1.4.

Use of mobile phones and risk of glioma and meningioma were published from Norway as part of the Interphone study (Klaeboe et al 2007). It included 289 (71 %) glioma cases, 207 (69 %) meningioma cases and 358 (69 %) controls. Significantly decreased OR = 0.6, 95 % CI = 0.4-0.9 was found for glioma and decreased OR = 0.8, 95 % CI = 0.5-1.1 for meningioma. For glioma 22 additional ORs were calculated using different exposure criteria as discussed above and all calculations yielded OR < 1.0, seven significantly so. Also for meningioma most ORs were < 1.0. Again these results indicate systematic bias in the study.

F. Meta-analysis

A meta-analysis of the risk for acoustic neuroma, glioma and meningioma was performed for mobile phone use with a latency period of 10 years or more (Hardell et al 2007). For acoustic neuroma studies by Lönn et al (2004), Christensen et al (2004) Schoemaker et al (2005) and Hardell et al (2006a) were included, all giving results for at least 10 years latency period or

more. Overall OR = 1.3, 95 % CI = 0.6-2.8 was obtained increasing to OR = 2.4, 95 % CI = 1.1-5.3 for ipsilateral mobile phone use (Lönn et al 2004, Schoemaker et al 2005, Hardell et al 2006). For glioma OR = 1.2, 95 % CI = 0.8-1.9 was calculated (Lönn et al 2005, Christensen et al 2005, Hepworth et al 2006, Schüz et al 2006, Hardell et al 2006b, Lahkola et al 2007). Ipsilateral use yielded OR = 2.0, 95 % CI = 1.2-3.4 (Lönn et al 2005, Hepworth et al 2006, Hardell et al 2006b, Lahkola et al 2007). In total OR = 1.3, 95 % CI = 0.9-1.8 was found for meningioma (Lönn et al 2005, Christensen et al 2005, Schüz et al 2006, Hardell et al 2006a) increasing to OR = 1.7, 95 % CI = 0.99-3.1 for ipsilateral use (Lönn et al 2005, Hardell et al 2006b).

IV. Discussion

This review included 20 studies, two cohort studies and 18 case-control studies. We recently made a review on this topic and more details can be found in that publication (Hardell et al 2007). Only two studies have been published since then. Both were on acoustic neuroma (Klaeboe et al 2007, Schlehofer et al 2007). They were small with no cases with a latency period of at least 10 years. Furthermore, most ORs were < 1.0 indicating serious methodological problems in the studies.

So far most studies have had no or limited information on long-term users. No other studies than from the Hardell group has published results for use of cordless phones (Hardell et al 2006a,b). As we have discussed in our publications it is pertinent to include also such use in this type of studies. Cordless phones are an important source of exposure to microwaves and they are usually used for a longer time period on daily basis as compared with mobile phones. Thus, to exclude such use seems to underestimate the risk for brain tumors from use of wireless phones.

It should be noted that the Hardell group has included also use of cordless phones, and thus in the exposure assessment the "unexposed" cases and controls have not been exposed to either cordless or cellular phones. This is in contrast to the Interphone study where the "unexposed" may have been exposed to cordless phones of unknown amount.

Of the 18 case-control studies 11 gave results for $\geq$ 10 years use or latency period. However, most of the results were based on low numbers. Thus, it is necessary to get an overview if there is a consistent pattern of increased risk with longer latency period and to make a formal meta-analysis of these findings. Since brain tumours are a heterogenic group of tumours it is reasonable to separate the results for malignant and benign tumours, as has been done in the various studies.

The Danish cohort study (Johansen et al, 2001) is not very informative due to limits in study design, analysis and follow-up. Schüz et al. (2006) reported an update of this previous study on mobile phone subscribers in Denmark. Since this report has gained substantial media coverage as "proof" of no brain tumor risk from mobile phone use we will discuss the shortcomings of the study in more detail in the following.

The cohort was established for persons that some time during 1982–1995 were registered cellular telephone users and has now been followed against the Danish Cancer Registry until 2002, seven years more than in the previous study. Previously (Johansen et al, 2001) 9 persons with brain tumors had used GSM phones for > 3 years, and OR =1.2 was reported. Now, data were not provided for type of phone or years of use. Rather the calculation of latency was based on first year of registration.

During early 1980s almost all cellular telephones were used in cars with external antennae. These subjects were unexposed to electromagnetic fields (EMF). No information regarding such use is provided, and one may assume that such participants are now included as exposed although they were not. Over 200 000 (32 %) company subscribers were excluded from the cohort. These are the heaviest users and are billed 4.5 times more than the layman in Sweden. They started use the earliest, but were included in the "non-user" group, i.e., the general Danish population.

SIR among cellular telephone users was 1.21 for temporal glioma (Schüz et al 2006), a region most exposed to EMF, based on 54 persons and not on phone type or time of first use (latency period). No information regarding the ear used and correlation with tumor site was given. The expected numbers were based on the general population. Because a large part of the population uses mobile phones and/or cordless phones, and the latter use was not assessed at all in the study, there is no truly unexposed group for comparison. Risk of cancer was underestimated, e.g., in the group with first use $\geq$ 10 years, the associated risk for brain tumors was low (SIR =0.7, 95 % CI = 0.4- 0.95). Relying on private cellular network subscription as measure of mobile phone use has been questioned (Ahlbom et al 2004, Funch et al 1996).

There seems to be a "healthy worker" effect in the study because of the decreased overall cancer risk (SIR= 0.9, 95 % CI = 0.9-0.95). Of the subscribers 85 % were men and 15 % women. Certainly early mobile phone users are not socioeconomically representative of the whole Danish population, used for comparison. The cohort only included people > 18 years of age. We reported (Hardell et al 2004, 2006a,b) that cellular telephone use beginning before age 20 is associated with a higher risk of brain tumours than use starting after age 20.

The authors do not acknowledge the contribution by the telecom industry as cited in the first publication (Johansen et al 2001), i.e., TelemarkDanmarkMobil and Sonofom. Two of the authors are affiliated with the private International Epidemiology Institute, Rockville, MD, USA, which has contributed financially to the study. Where the International Epidemiology Institute gets its money from is not declared. In the application to the Danish National Mobile Phone Program, which funded part of the study, no mention of the involvement or payment of these two consultants was made, a fact that is now being set under question.

Regarding the case-control studies there seems to be a consistent pattern of an increased risk for acoustic neuroma using a 10-year latency period and considering ipsilateral exposure. It might be a "signal" tumour type for increased brain tumour risk from microwave exposure, since it is located in an anatomical area with high exposure during calls with cellular or cordless phones (Hardell et al, 2003). Christensen et al (2004) found no association using a $\geq$ 10 year latency period, but the result was based on only 2 cases. Interestingly, the tumours were significantly larger in the total group of regular mobile phone users.

In our study we found an increased risk also with shorter latency period than 10 years (Hardell et al 2006a). However, it is not known at what stage in the carcinogenesis microwaves act. An effect might exist at different stages both of promoter and initiator type. We conclude that the results on acoustic neuroma are consistent with an association with use of cellular phones using a latency period of $\geq$ 10 years.

Regarding meningioma no consistent pattern of an association was found, although ipsilateral exposure in the $\geq$ 10 years latency group increased the risk in the meta-analysis. For a definite